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

Period: January 1, 2012 - December 31, 2015

1. Basic information on the institute:

1.1. Legal name and address

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

Address till January 1, 2016:
Cancer Research Institute
Slovak Academy of Sciences
Vlárska 7
833 91 Bratislava
Slovak Republic

1.2. URL of the institute web site

www.exon.sav.sk

1.3. Executive body of the institute and its composition

Directoriat	Name	Age	Years in the position
Director	Ján Sedlák, D.Sc Lucia Kučerová, Ph.D.	59 43	2007-03/2015 04/2015-
Deputy director	Miroslav Piršel, Ph.D. Lucia Kučerová, Ph.D. Miroslav Chovanec, Ph.D.	65 43 47	2007-2013 2014-03/2015 2014-
Scientific secretary	Alena Gábelová, Ph.D.	61	2007-

1.4. Head of the Scientific Board

Miroslav Chovanec, Ph.D.

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	63,0	46,180	63,0	45,520	60,0	50,350	60,0	45,710	**246,0**	**61,5**	**46,940**
Number of PhD students	15,0	15,000	17,0	17,000	14,0	14,000	14,0	14,000	**60,0**	**15,0**	**15,000**
Total number	78,0	61,180	80,0	62,520	74,0	64,350	74,0	59,710	**306,0**	**76,5**	**61,940**

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

Research staff	2012		2013		2014		2015		average	
	No.	FTE	No.	FTE	No.	FTE	No.	FTE	No.	FTE
Institute in whole	77,0	46,180	76,0	45,520	75,0	50,350	76,0	45,710	**76,0**	**46,940**
Laboratory of Molecular Genetics	15,0	9,620	13,0	8,620	0,0	0,000	0,0	0,000	**14,0**	**9,120**
Laboratory of Cancer Genetics	9,0	8,080	10,0	9,080	0,0	0,000	0,0	0,000	**9,5**	**8,580**
Laboratory of Mutagenesis and Carcinogenesis	16,0	11,300	18,0	11,610	0,0	0,000	0,0	0,000	**17,0**	**11,455**
Laboratory of Molecular Oncology	18,0	13,550	14,0	11,750	0,0	0,000	0,0	0,000	**16,0**	**12,650**
Laboratory of Tumor Immunology	12,0	9,930	13,0	11,610	0,0	0,000	0,0	0,000	**12,5**	**10,770**
Laboratory of Radiobiology	7,0	6,330	8,0	8,000	0,0	0,000	0,0	0,000	**7,5**	**7,165**
Department of Genetics	0,0	0,000	0,0	0,000	40,0	30,860	39,0	28,290	**39,5**	**29,575**
Department of Molecular Oncology	0,0	0,000	0,0	0,000	35,0	31,410	37,0	30,670	**36,0**	**31,040**

1.6. Basic information on the funding of the institute

Institutional salary budget and others salary budget

Salary budget	2012	2013	2014	2015	average
Institutional Salary budget *[thousands of EUR]*	**802,1**	**802,6**	**792,1**	**853**	**812,450**
Other Salary budget *[thousands of EUR]*	**85,8**	**106**	**101,6**	**112,8**	**101,550**

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

1. Scientific and research activities of the Cancer Research Institute (CRI) are focused on basic research of etiopathogenetic factors and mechanisms leading to conversion of normal cells to malignant tumour cell population and molecular mechanisms of this conversion. It concerns characteristics of biological, biochemical, immunological, molecular-biological and genetic features and phenotypic characteristics of tumour cells from the perspective of oncology, normal and pathologic physiology, molecular biology, biochemistry and cytology.
2. CRI contributes to solving of serious and for medical practise important issues related to development and the use of diagnostic and therapeutic procedures, biopreparates and drugs for prevention and treatment, as well as new technologies for improvement of diagnosis in certain types of cancer disease.
3. CRI pursues consultancy and expertise services related to major activity of the Institute.
4. CRI carries out PhD study program in the frame of the general valid and legal rules.
5. CRI performs edition and publishing activity for provision of publication of outcomes of scientific and research activity via printed and electronic media.
6. CRI realizes the popularisation of research and development outcomes.

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

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

Main research activities of the CRI SAS during the assessed period were:

1. **DNA Repair, Genome Stability, Chromosome Dynamics & Cancer**
2. **Nanomaterials for Therapeutic Applications: Nano:Bio Interactions and Biosafety**
3. **Cancer Biomarkers, Radiobiology and Cancer Risk Assessment**
4. **Microbiome and Cancer**
5. **Antitumour Signalling Pathways Triggered by the Natural Compounds**
6. **Antitumour Gene Therapy Directed by Engineered Mesenchymal Stromal Cells**
7. **Tumour Microenvironment, Intratumour Heterogeneity and Cancer Stem Cells**

1. *DNA Repair, Genome Stability, Chromosome Dynamics & Cancer*

An accumulating body of evidence shows a key role of DNA damage response and repair pathways in cancer. Correlation between defects in these mechanisms and higher cancer incidence in affected individuals has been well-documented. In addition, DNA damage response and repair pathways may have implications on cancer treatment, so that new treatment modalities for cancer can be exploited based on their detailed knowledge. Therefore, our research interest has been focused on the understanding of molecular details of mechanisms of genome integrity maintenance, as well as of clinically important DNA damage and repair pathways. Studied DNA repair pathways include three forms of excision repair, nucleotide excision repair (NER), base excision repair (BER) and mismatch repair (MMR), two main DNA double-strand break (DSB) repair mechanisms, homologous recombination (HR) and non-homologous end-joining (NHEJ), and interstrand cross-link (ICL) repair that involves action of several separate DNA repair pathways and is co-ordinated and regulated by Fanconi anemia (FA) DNA damage and response pathway. In addition, there are DNA damage types that rather undergo direct reversal than repair process *per se*. This includes demethylation, oxidative demethylation and photoreactivation reactions. DNA damage tolerance and avoidance mechanisms such as translesion DNA synthesis (TLS) also operate in damaged cells. Alterations or abnormally high-frequency of errors during processes involved in cell division, such as DNA replication and repair, splicing, kinetochore assembly and attachment, chromosome segregation or cytokinesis would also cause genome instability and are related to cancer.

Prototypical FA-related pathway in yeast (PI: Miroslav Chovanec)
Efficient repair of ICLs is essential to maintain genome stability and cell viability. FA is a recessive genetic disease, associated with genomic instability and defects in ICL repair. This pathway has not been thought to be conserved in the budding yeast *Saccharomyces cerevisiae*, and although the yeast Mph1 helicase is a putative homolog of FANCM, yeast cells lacking Mph1 are not sensitive to ICLs. However, our results suggest that a prototypical FA-related ICL repair pathway operates in budding yeast, which acts redundantly with the pathway controlled by Pso2, and is required for the targeting of Exo1 nuclease to chromatin to execute ICL repair. Based on our and other's data, we brought a model how prototypical FA-related pathway operates in yeast to maintain stability of their genomes [PLoS Genetics 2012, 8 (8):e1002884; Cell Cycle 2012, 11:3739-3744].

Lif1 SUMOylation and its Role in NHEJ (PI: Miroslav Chovanec)
DSBs are also considered to be very severe form of DNA damage. In similar manner to ICLs, DSBs can cause cell death if unrepaired, as well as promote processes leading to mutagenesis and tumourigenesis, if misrepaired. Hence, effective DSB repair is crucial to maintain genome stability and cell viability. Our findings suggest that the SUMOylation of the Lif1 represents a new regulatory mechanism that downregulates NHEJ in a cell cycle phase-independent manner [Nucleic Acids Research 2013, 41:5341-5353].

Post-translational Regulation of Chromosome Segregation (PI: Ľuboš Čipák)
Protein phosphorylation is one of the major mechanisms by which cellular processes are regulated. Using fission yeast *Schizosaccharomyces pombe*, we studied the biological relevance of protein phosphorylation for the maintenance of genome integrity focusing on regulation of the proteins involved in processes of chromosome segregation. We showed that Hhp1 and Hhp2 protein kinases phosphorylate Rec11 cohesin subunit, which allows the loading of linear element proteins at DSB hotspots to promote meiotic DSB formation and recombination. Our results provide novel insights into the regulation of chromosomal features required for crossing-over and successful reproduction [PLoS Genetics 2015,11(5):e1005225; Nature Protocols 2014, 9:223-331].

Role of NF1 in the Expression of Genes Regulated by Cellular Stress (PI: Katarína Luciaková)
Oxidative stress and persistent activation of DNA damage response (DDR) are causally involved in development of cellular senescence, a phenomenon implicated in fundamental (patho)physiological processes such as ageing, foetal development and tumourigenesis. Here, we report that adenine nucleotide translocase-2 (ANT2) is consistently down-regulated in all three major forms of cellular senescence: replicative, oncogene-induced and drug-induced, in both normal and cancerous human cells. siRNA-mediated knock-down of *ANT2* in proliferating cells resulted in increased levels of reactive oxygen species (ROS) and activation of the DDR [Neoplasma 2013, 60:233-239; Cellular Signaling 2014, 26:2903-2911].

2. *Nanomaterials for Therapeutic Applications: Nano:Bio Interactions and Biosafety*

Progress in biomedical nanotechnologies made in recent years has led to increased applications of the nanomaterials in clinical practice. Nanobiotechnology has already been providing earlier diagnosis, treatments, and improved imaging to better, more efficient, and more targeted therapies for many diseases. Inorganic nanomaterials (INMs) like for example iron oxide or gold have received increased attention in the recent years as potential diagnostic and therapeutic tools in modern medicine. Nanoparticle cores can be designed to retain unique physico-chemical properties (optic, magnetic *etc.*) that are not possible to reach with the traditional nanomaterials like liposomes, dendrimers or polymers. These properties make INMs useful imaging contrast agents for

noninvasive diagnostic and prospective theranostics. Although the benefit of INMs is obvious, their impact on basic cellular processes such as cell cycle, cell signalling, apoptosis, oxidative stress or inflammation has not been sufficiently explored. There is a gap of knowledge about the molecular and cellular mechanisms involved in INMs interactions, about deposition of INMs in the tissues or immunological responses. A complex toxicity assessment is hence necessary to address the biosafety of these nanoparticles. The new generation of nanomedicines is focused on active targeting, *i.e*. the drug is delivered directly into cancer cells or subcellular compartments. For these reasons understanding the mechanisms of nanoparticles entry and trafficking, and characterization of factors influencing these processes, are highly actual. Moreover, investigation of the nano:bio (nanomaterial:cell) interactions allows the development of a new generation of multifunctional nanoparticles for specific clinical purposes.

Molecular and Cellular Interactions of Magnetic Nanoparticles with Human Cells and Mechanism of Uptake (PI: Alena Gábelová)
The human lung adenocarcinoma epithelial (A549) cells and the human embryo lung (HEL 12469) cells were used to investigate the uptake, cytotoxicity and genotoxicity of magnetite nanoparticles (MNPs) with different surfaces modifications. All MNPs, regardless of the coating, induced significant levels of DNA breakage in A549 cells but not in HEL 12469 cells. Our data indicate that oxidative stress plays, at most, only a marginal role in the genotoxicity of surface-modified MNPs in human lung cells.
The determination of internalized amount of nanoparticles in cells is essential for quantitative particle toxicology and pharmacology. Moreover, understanding of the mechanism(s) underlying nanoparticle`s uptake and factors which influence this process is crucial for development adequate nanocarriers for targeted delivery. Our results showed that the process of internalization is influenced by both the physico-chemical properties of nanoparticles (*e.g*. particle size and surface chemistry/coating) and by the origin of cells (normal *vs*. tumor cells) [Neoplasma 2012, 59:584-597; Toxicology Letters 2014, 226:303-313].

Functional Consequences of Gold and Magnetic Nanoparticle Uptake by Renal Cells (PI: Andrea Bábelová)
Kidney is one of the main organs targeted by nanoparticles (NPs) participating in their excretion out of the body. Combination of biological and physico-chemical approaches to this issue will contribute to novel information about i) the degree of nanoparticle internalization into the mesangial cells and podocytes, ii) the shift in the distinct gene expression pattern induced by NPs, iii) cell damage induced by NPs (cytotoxicity, renotoxicity), thereby allowing iv) characterization and comparison of physical and chemical parameters of gold and iron oxide NPs in biological system. The first results show indeed nanoparticle-induced damage in podocytes that will be investigated further together with other goals of this just freshly started project [SASPRO_0084-01-02, 2015; VEGA 2/0113/15, 2015].

Enhanced Bioavailability of Realgar Nanoparticles: Paired Comparison with ATO-induced Signaling (PI: Ján Sedlák)
In recent years, realgar (α-As4S4), an arsenic sulfide mineral, has exhibited significant beneficial effects in the treatment of acute promyelocytic leukaemia, chronic myeloid leukemia, and even some human malignancies, especially skin and lung cancer. The main obstacle of realgar use in clinical practice is its insolubility in water and most organic solvents, resulting in poor bioavailability. We studied nanosize crystals, that dramatically enhance realgar`s bioavailability and extend their clinical use. We used realgar (As_4S_4) nanoparticle (NP) suspension for treatment of melanoma cell lines. NP realgar increased intracellular glutathione level, mediated by the upregulation of NRF2 mRNA as well as its downstream target heme oxygenase-1. Data obtained suggest that NP realgar is

comparably or even more effective than arsenic trioxide (ATO) and that due to advantages of its nanoparticle formulation it can potentially replace ATO in the therapeutic applications. [Neoplasma 2014; 61:700-709].

3. *Cancer Biomarkers, Radiobiology and Cancer Risk Assessment*

Cancer is a multifactorial disease which arises as a result of mutational and epigenetic changes. One of the main goals in cancer research is finding of biomarkers for early detection of disease and its recurrence, allowing personalized approach in cancer treatment. A few fundamental issues such as tumour heterogeneity, a highly dynamic nature of the intrinsic and extrinsic determinants of radio- and chemoresistance, along with the plasticity and diversity of cancer stem cells (CSC) make biomarker development a challenging task. The intriguing topic in biomarker discovery is a concept of liquid biopsy, i.e. to look for these markers in peripheral blood or in other sources that can be non-invasively sampled such as urine, stool, tears, or saliva. A biomarker is ultimately defined not by its biological process or mechanism but by its ability to predict a clinical response in a robust manner. Biomarker discovery was realized at CRI SAS using various approaches such as assessment of genetic polymorphisms, oncogenic gene fusions, DNA repair markers, circulating tumour cells (CTC), cell-free circulating tumour DNA, shedded immune molecules, urine autofluorescence, differentiation marker pattern, cytokine profiles, and analysis of CSC-specific markers for tumour radiosensitivity. Discovery of new tumour-specific biomarkers in different specimens facilitates implementation of personalized medicine strategies.

DNA Methylation Profiles Associated with Invasivity and Metastasis Regulation in Breast Cancers (PI: Ivana Fridrichová)

We investigated the pathogenic changes in DNA methylation in relationship to the cancer development. We have introduced quantitative methods (QM-MSP and pyrosequencing) for evaluation of DNA methylation profiles in specific genes participating in partial processes of breast tumourigenesis. The aim of our studies was to identify DNA methylation patterns in breast tumours that could be potentially utilized for more precise diagnostics and more targeted therapy. Our results indicate that *RASSF1A* methylation, universal cancer marker, correlate with percentage of cancer cells expressing ER and PR that could be useful for the prognosis of hormonal therapy response. Furthermore, the risk for lymph node metastases development and higher proliferation of cancer cells was increased by hypermethylation of *CXCL12* and *ADAM23* genes; therefore, the quantification of methylation levels in these two genes could be useful for monitoring of metastatic potential [Cancer Biomarkers 2012, 10:13-26; Translational Oncology 2013, 6:297-304; Neoplasma 2013, 6:635-646; Translational Research 2015, 165:717-730].

Dynamics of Epigenetic Changes during Epithelial-to-Mesenchymal Transition Induced by Mesenchymal Stromal Cells *in vitro* (PIs: Božena Smolková, Tomáš Krivulčík)

We analyzed dynamics of global and gene specific DNA methylation changes and histone modifications during Epithelial-to-mesenchymal transition (EMT). Our data demonstrate the ability of AT-MSCs to induce EMT *in vitro*. Changes in DNA methylation were not detectable in early phases of EMT therefore we hypothesise that they could be rather a marker of the sustained presence of potent EMT-inducing signals. Several lines of evidence have shown that histone modifications precede DNA methylation changes during EMT. Therefore we have focused on possible EMT-related histone modifications that are currently under investigation [Neoplasma 2016; under revision].

Genotoxic effects of non-ionizing electromagnetic radiation (PI: Igor Belyaev)
While extremely low frequency and radiofrequency electromagnetic fields were classified by the IARC as carcinogen group 2B, the mechanisms of EMF effects remain elusive. We focus on these mechanisms and molecular markers for analyzing EMF effects and cancer risk assessment in *in vitro* and epidemiological studies [Electromagnetic Fields in Biology and Medicine, M. Markov, ed. (Boca Raton, London, New York, CRC Press), pp 49-68, 2015; In: Bioelectromagnetics and Subtle Energy Medicine, P.J. Rosch, ed. (Boca Raton, London, New York, CRC Press), pp 517-539, 2015].

Implementation of Radiobiological Research in Radiotherapeutical Practice (PIs: Igor Belyaev, Eva Marková)
Proteins involved in the formation of ionizing radiation induced foci (IRIF), such as tumor protein p53 (TP53) binding protein 1 (53BP1) and phosphorylated histone 2A family member X (γH2AX), are considered to be the most sensitive molecular markers for DSB detection. We developed sophisticated experimental techniques to efficiently enumerate IRIF using imaging flow cytometry, laser confocal and fluorescent microscopy and validated their application for assessment of individual radiosensitivity of cancer patients and relative biological efficiency of proton therapy [International Journal of Radiation Biology 2013, 89:301-309; International Journal of Radiation Biology 2013, 89:716-723, Neoplasma 2015, 62:770-776; International Journal of Radiation Biology 2015, 91:1-12; Cytometry A 2015, 4:227-231;].

DNA Damage Response and Preleukemic Clones in Hematopoietic Stem Cells in Diagnostics, Risk Estimation and Treatment of Paediatric Leukemia (PIs: Igor Belyaev, Milan Škorvaga)
A chromosomal translocation resulting in an *in-frame* preleukemic gene fusion (PGF) is often a primary genetic abnormality in the origination of acute childhood lymphoblastic/myeloid leukaemia (ALL/AML). PGF arise in haematopoietic stem/progenitor cells (HSPC), often *in utero*. According to our results, about 1% of Slovak newborns harbour most frequent PGF in their umbilical cord blood while only those PGF may result in overt leukaemia that arise in specific HSPC subpopulations with leukemogenic potential. We validated the application of multiplex reverse transcription-polymerase chain reaction (RT-PCR) assay for molecular diagnosis of the most common paediatric acute lymphoblastic leukaemia-associated fusion transcripts. This screening may provide a reliable, specific and sensitive method amenable to a standard laboratory practice and a cost-effective alternative to more complex and expensive RT qPCR techniques [Neoplasma 2014, 61:617-625; PLoS ONE 2014; Neoplasma 2014, 61:758-765].

Multiparameter Flow Cytometry Immunophenotyping (MFCI) is an Essential Tool for the Diagnostic and Monitoring of Patient Response to Therapy (PIs: Ján Kusenda, Michaela Fajtová)
MFCI represents a convenient tool for the assessment of the leukaemia-associated immunophenotype (LAIP) which is the most suitable for minimal residual disease (MRD) monitoring. It provides evidence of the new prognostic factors as well as of MRD confirmation in patients with leukemia before and past allogenic transplantation. MRD monitoring by MFCI can serve as a central stratification parameter in future clinical trials [Neoplasma 2014, 61:119-127].

Identification of aberrant erythroid development in acute erythroid leukemia or myelodysplastic syndrome [PI: Michaela Fajtová]
In-depth multiparameter fow cytometry immunophenotyping of nucleated erythroid progenitors during bone marrow regeneration revealed that the expression of CD105 and CD117 is critical for the distinction between 4 phenotypically different developmental stages of nucleated erythroid progenitors: pro-erythroblasts, basophilic erythroblasts, polychromatophilic erythroblasts and orthochromatophilic erythroblasts. CD105 antigen expression was specifically associated with pro-

erythroblasts and basophilic erythroblasts, whereas CD117 was expressed at the earliest pro-erythroblast stage [Leukemia and Lymphoma 2013, 54:2523-2530].

Soluble HLA-G Antigens (sHLA-G1 and sHLA-G5) in Human Pathology (PI: Katarína Poláková)
We analysed sHLA-G molecules in the blood of patients with B-CLL leukemia. We found, that the most of B-CLL patients contained total sHLA-G, while HLA-G5 antigen was detected only in few cases. We assume that the majority of sHLA-G present in blood is generated by proteolytic cleavage of membrane-bound HLA-G1 isoform. Importantly this study confirmed that HLA-G5 molecules have no clinical significance for B-CLL leukaemia [Leukemia Research 2013]. In the early post-transplant period (1-2 weeks) the pre-transplantation sHLA-G levels decreased at the majority of patients. After extended post-transplantation period, a substantial increase of sHLA-G was detected [Immunobiology 2015]. Serum sHLA-G values were significantly higher in patients with stable allograft function than with acute rejection. This observation supports assumption that the increase of serum sHLA-G may contribute to allograft acceptance [Transplantation Immunology 2015].

Modulation of Immunological Parameters during the Course of MGN-3 Arabinoxylan Consumption by Multiple Myeloma Patients – Placebo Controlled Study (PI: Dana Cholujová)
The randomized, placebo controlled study was performed to examine the effects of MGN-3 on innate immune system in multiple myeloma patients. Our results demonstrate a clear increase in NK activity in MGN-3-treated patients compared to the placebo group, an increased level of myeloid DCs in peripheral blood, and augmented concentrations of T helper cell type 1-related cytokines. Our results suggest that MGN-3 may represent an immunologically relevant product for activating innate immunity in multiple myeloma patients [Cancer Immunology and Immunotherapy 2013, 62:437-445].

Fluorescence Analysis of Urine and its Potential for Ovarian Cancer Screening (PI: Ľuba Hunáková)
Human urine is a complex biological fluid containing a range of chemical compounds produced by the body. We analysed changes in urine autofluorescence from patients with ovarian cancer, exploring the differences in fluorescence characteristics of urine between healthy subjects and patients with ovarian cancer. Concentration matrices of synchronous spectra (CMSS) were used to classify samples. CMSS analysis allowed us to distinguish patients with malignant tumours from healthy ones with a high sensitivity (91.67 %) and specificity (100 %) [Neoplasma 2013, 60:533-537; Journal of Photochemistry and Photobiology B: Biology 2015, 153:191-197; Neoplasma 2015, 62:500-506].

4. *Microbiome and Cancer*

The microbiome as the collective genetic material of the microflora, over exceed the number of genes in the human genome and is unique for each individual. Currently, Human Microbiome Project (HMP) belongs to the most comprehensive research projects worldwide enabling characterization of the human microbiota and analysis of their role in human health and disease. Due to the benefits providing for the host and mainly for immediate interaction with the host immune system, a gastrointestinal microflora can be considered "cardinal microbiome". Favourable, but also negative effects of bacteria on the host microorganisms' physiology are still not well determined.

Increasing incidence and mortality of colorectal cancer brings the necessity to uncover new possibilities in the prevention, diagnosis and treatment. Several studies focused on differences between the bacterial composition of healthy individuals and colorectal cancer patients confirmed that the intestinal microflora constitution and structure could lead to the colorectal polyps-premalignant development. Growing evidence suggests that the colonic microflora play a critical role in regulating several host functions important to tumour formation such as intestinal epithelial

cell homeostasis, barrier function, mucosal immune responses, and host metabolism. Modification of microflora imbalance might represent the future direction in prevention and even treatment of gastrointestinal cancers. Experimental and clinical studies have shown that dysbiosis in gastrointestinal microflora can be modulated by the effect of probiotics. Probiotics might have beneficial effects on some aspects of toxicity related to anticancer treatment especially radiation therapy. Current evidence supporting the probiotic use as adjunctive therapy to anticancer treatment is limited, especially in cancer patients treated with chemotherapy.

Studying the Role of Gut Microflora in Familial Adenomatous Polyposis (FAP) and Colorectal Cancer (PIs: Vladimír Zajac, Soňa Čierniková.)
Alternative gene therapy using bacterial vectors for delivery of the therapeutic protein molecules could represent one of the cancer prevention possibilities [Neoplasma 2015, 62:345-352]. Recombinant bacteria carrying plasmid with complete *APC* gene sequence were orally administered to APC+/APC 1638N mice with mutations in the *APC* gene. All transgenic mice without therapy developed adenomatous polyps in the gastrointestinal tract. Transgenic mice treated by oral administration of bacteria expressing functional APC protein developed polyps in 33.3% [Neuro-Endocrinology Letters 2012, 33:26-33]. Enormous size of the human microbiome and intimate proximity between intestinal bacteria and colon epithelial tissue raises the question of opportunity for horizontal gene transfer to somatic cells. Analyses of bacteria isolated from familial adenomatous polyposis (FAP) patients revealed the presence of APC-like sequences showing more than 90% sequence homology with human Adenomatous polyposis coli (*APC*) gene [Medical Science Monitor 2012, 18:486-492, Neoplasma 2014, 61:283-290].

Probiotics and Colorectal Cancer (PIs: Vladimír Zajac, Soňa Čierniková)
A randomized, double blind, placebo controlled pilot study, suggested that administration of probiotic formula Colon Dophilus™ compared to placebo was associated with reduction of gastrointestinal toxicity of irinotecan based chemotherapy, and these results were consistent for all types of recorded gastrointestinal toxicity [Complementary Therapies in Medicine 2013, 21:712-723; Complementary Therapies in Medicine 2015, 23:356-362].

The Role of Bacteria in a Syndrome of Acquired Immunodeficiency (PI: Vladimír Zajac)
Human immunodeficiency virus type I (HIV-1) is widely accepted as the cause of AIDS, sufficient to cause immunodeficiency and to destroy parenchyma cells inducing the widespread organ failure. Despite unquestionable success in the diagnostics and therapy of this disease, it is still not possible to stop the worldwide pervasion of AIDS, especially in Africa and Asia. It is necessary to deliberate other potential factors, not only HIV, which may take part in aetiology of the disease. There is increasing evidence pointing out that GIT and other mucosal tissue, and not the blood, is the main place of HIV infection and CD4+T cell loss. Recent results showed that a major area of memory CD4+ T cells destruction by simian immunodeficiency virus (SIV) is in mucosal cells, where most of T cells expressing CD4 reside. The loss of $CD4^+$ T cells in the intestine occurred coincident with the productive infection of large numbers of mononuclear cells at this site. These findings support the idea, that the mucosal and intestine immune system is the major site of viral replication [Journal of Antivirals and Antiretrovirals 2013, S15:1-6, Neuro-Endocrinology Letters 2014, 35:101-106; Journal of Vaccines and Vaccination 2014, 5:4;].

5. *Antitumour Signaling Pathways Triggered by the Natural Compounds*

A large proportion of conventional and novel anti-cancer agents are derived from natural products. Although numerous studies suggest that natural compounds are very beneficial to human health and may decrease the risk of many types of cancer, some contradictory results were gained

in epidemiological and molecular-epidemiological studies. This fact stimulated a great need for more and deeper knowledge about the role of natural compounds on different levels of living systems. By their nature, these compounds are generally low molecular weight substances with various biological activities as antioxidants/redox modulators, antibacterial, anti-inflammatory, immunomodulatory, antiangiogenic and anticancer substances. Among them, natural isothiocyanates, polyphenols, phenylpropanoids, several components of essential oils and even inorganic forms of selenium (Se) and tellurium (Te) are tested as medically interesting compounds.

Sulforaphane Reduces Molecular Response to Hypoxia and Chemoresistance (PIs: Ľuba Hunákova, Ján Sedlák)
We evaluated the effect of clinically achievable concentrations in serum of sulforaphane (SFN) for the treatment of ovarian carcinoma cell line A2780 and its two derivatives, adriamycin-resistant A2780/ADR and cisplatin-resistant A2780/CP cell lines exposed to hypoxia (2% O2). SFN decreases the level of HIF-1α protein without affecting its transcription and stability. It can also diminish transcription and protein level of the HIF-1 target, CA IX, which protects tumor cells from hypoxia-induced pH imbalance and facilitates their migration/invasion. While SFN significantly potentiated cisplatin-induced DNA damage in A2780 cells, it protected SKOV3 cells against cisplatin-crosslinking. We revealed a less efficient Nrf-2 pathway inducibility by sulforaphane in A2780 compared to SKOV3 cells. Different activation of the Nrf-2 pathway may explain the dual effects of sulforaphane [Toxicology Letters 2014, 230:479-486; International Journal of Oncology 2015, 47:51-60].

Chemoprotective Effects of Natural Compounds (PI: Katarína Kozics)
We focused on the protective potential of plant extracts from *Salvia officinalis*, *Thymus vulgaris*, *Lavandula angustifolia* and *Rosmarinus officinalis* in experimental systems *in vitro* and *ex vivo*. Based on our results studied plant extracts manifested antioxidant activity and protective effects against oxidative damage [Food Chemistry 2013, 141:2198-2209; Neoplasma 2014, 60:585-597; Mutagenesis 2015, 31:51-59].

DNA-protective Activity of Plant Essential Oils (PI: Eva Horváthová)
We studied the ability of selected genotoxins and carcinogens to induce genotoxic effects in cells either cultivated *in vitro* or isolated from different organs of rats, as well as the ability of selected natural substances to reduce or to eliminate these perilous cellular effects in different types of mammalian cells. Selected components of plant essential oils and intact *Rosmarinus officinalis* oil were investigated for their antioxidant, iron-chelating, and DNA-protective effects [Mutagenesis 2012, 27:581-588; Mutation Research 2013, 757:15-22; Journal of Agricultural and Food Chemistry 2014, 62:6632-6639; Neoplasma 2015, 62:722-732].

Mechanisms of Selenium and Tellurium Toxicity in Yeast (PI: Miroslav Chovanec)
As sodium selenite (SeL), inorganic Se form, has been a part of many studies and this Se form has also been used as a dietary supplement by the public, we investigated mechanisms of SeL-induced toxicity in yeast. We proposed that SeL-induced toxicity markedly results from DNA injury, thereby highlighting the importance of DNA damage response and repair pathways in protecting cells against the toxic effects of this Se compound. In addition to Se, toxic effects of another redox-modulating agent, Te, have been examined. [Chemical Research in Toxicology 2012, 25:1598-1608; Tetrahedron 2012, 68:10577-10585; Molecules 2014, 19:12258-12279].

6. *Antitumour Gene Therapy Directed by Engineered Mesenchymal Stromal Cells*

In the last five years we examined in detail an antitumour effect of engineered and/or prodrug-converting mesenchymal stromal cells (MSCs) on hard-to-treat human tumour types. Engineered MSCs served for targeted delivery of the agents of interest because of their unique ability to home and engraft at the sites of tumour growth and intrinsic resistance. Previously we introduced two types of suicide genes encoding prodrug converting enzymes (yeast fusion CD::UPRT, HSVtk) and apoptosis inducing gene (TNFα) into the MSCs by retrovirus vector. Engineered MSCs were shown to achieve high antitumour effect on several animal models of human malignant disease (glioblastoma multiforme, metastatic melanoma, triple-negative breast carcinoma, chemoresistant medullary thyroid carcinoma). Our therapeutic approach and the combination of enzyme with non-toxic prodrug resulted in long-term control of subcutaneous xenograft growth. We were also able to achieve high rate of complete eradication of tumours, eradication of tumour cells on mouse model of experimental lung metastases and tumour-free survival in a proportion of rats bearing orthotopic glioblastoma. Improved optimized experimental setup as well as combination therapy of the two approaches (CD::UPRT/5FC plus HSVtk/GCV) showed stronger, synergic antitumour effect in the treatment of metastases and represents promising tool in the experimental cancer treatment.

Stem Cell–Mediated Prodrug Gene Therapy of Glioblastoma and Prostate Carcinoma (PIs: Veronika Altanerová, Čestmír Altaner)

In pre-clinical studies we evaluated the therapeutic efficacy of human mesenchymal stromal cells derived from bone marrow and from adipose tissue, engineered to express the suicide gene cytosine deaminase::uracil phosphoribosyltransferase to treat intracerebral rat C6 glioblastoma in a simulated clinical therapeutic scenario. Direct injections of therapeutic stem cells into the brain tissue surrounding the postoperative resection cavity led to a curative outcome in a significant number of treated animals [International Journal of Cancer 2012, 130: 2455-2463; Atlas Genet Cytogenet Oncol Haematol. 2012; 16: 757-764, International Journal of Cancer 2014, 134:1458-1465; Chapter “Stem Cell–Mediated Prodrug Gene Therapy of High-Grade Brain Tumours” in a book“Stem Cell Therapeutics for Cancer”, Edited by Khalid Shah. Harvard Medical School, Boston, Massachusetts, USA, Published 2013 by John Wiley & Sons, Inc, 2014]. Mesenchymal stem cells expressing therapeutic genes induce autochthonous prostate tumour regression [European Journal of Cancer 2014, 50:2478-2488].

Mechanism of Action and Synergy of Combined Gene-Directed Enzyme/Prodrug Therapy Mediated by MSCs (PIs: Miroslava Matúšková, Lucia Kučerová)

We tested the efficacy of MSCs-mediated gene therapy on tumour types which do not response to conventional therapy, as well as we focused on factors which influence the therapeutic outcome. We observed significant differences in response to the particular therapeutic approaches, and we demonstrated that gap-junctional intercellular communication, expression of enzymes involved in drug metabolism and ABC transporters influenced the outcome of the treatment [Journal of Gene Medicine 2012, 14 :776-887; Journal of Experimental and Clinical Cancer Research 2015, 34:33; Gene Therapy 2014, 21:874-887; Neoplasma 2015, 62:521-530].

Suicide Cytotoxicity and Bystander Effect of CD::UPRT/5-FC Therapy in Human Medullary Thyroid Carcinoma (PIs: Martina Poturnajová, Lucia Kučerová)

Medullary thyroid carcinoma (MTC) of parafollicular thyroid C-cells is resistant to radio- and chemotherapy. We have tested the efficiency of the gene-directed enzyme/prodrug therapy on human MTC-derived cell line TT. Our experiments confirmed the capability of the gene-directed enzyme/prodrug therapy by CD::UPRT/5FC to mediate strong cytotoxic and local bystander effect accompanied by significant antitumour effect in the absence of any toxicity *in vivo*, even though only

a small part of the tumour expressed transgene [American Journal of Pathology 2014, 184:953-965; Cancer Letters 2013, 335:299-305; Neoplasma 2013, 60:111-120].

Apoptosis-Inducing Mesenchymal Stromal Cells in Experimental Cancer Gene Therapy (PI: Silvia Tyčiaková)
Cell-based experimental anticancer therapy using mesenchymal stromal cells (MSCs) engineered to express therapeutic genes has a potential to inhibit tumour growth. TNFα as a pleiotropic cytokine can induce apoptosis of tumour cells, enhance immune response and can have tumour destructive capacity in selected tumour types. Retrovirally transduced MSCs (MCSs/TNFα) are able to constitutively secrete human TNFα protein from the transgene without change. In our experiments MSCs/TNFα significantly inhibited the tumour growth when coinjected together with melanoma cells subcutaneously and decreased the tumour penetrance to 50% [Journal of Gene Medicine 2015, 17:54-67].

7. *Tumour Microenvironment, Intratumour Heterogeneity and Cancer Stem Cells*

Recent data revealed an unexpected complexity within tumours. This diversity exists across the subsets of the tumour cells within the same tumour. Intratumoural heterogeneity plays a key role in the intrinsic and acquired chemoresistance to cytotoxic and targeted therapies. We focus on the molecular characterization of subpopulations of cells with increased chemoresistant and tumourigenic properties (cancer stem cells). Alternations in secretome, gene expression and signaling were studied; recently we were able to confirm that pharmacological and molecular inhibition of putative cancer stem cell marker such as ALDH1 enzyme affected chemoresistant phenotype. There is also important contribution of non-malignant cells and stroma surrounding each tumour, which significantly contribute to tumour behaviour. This non-malignant component of the tumour entitled tumour microenvironment is formed by subsets of cancer-associated fibroblasts, mesenchymal stromal cells, pericytes, endothelial cells, immune cells and extracellular matrix. The mutual interactions between tumour and non-malignant stromal cells can be responsible for many aspects of tumour biology including therapeutic resistance and contribution to stem cell compartment. Potential role of activated stromal fibroblasts and chronic low-level inflammation via nemosis, a programmed process of cell activation, in guiding tumour progression towards dormancy, is also one of the research interests in our group.

Role of Human Mesenchymal Stromal Cells in Tumour Microenvironment and Drug Resistance of Tumours (PI: Lucia Kučerová)
We focus on the non-malignant compartment of solid tumours designated tumour microenvironment (TME), which further increases the diversity of tumour cell phenotypes. Multipotent MSCs represent one of many stromal cell types in TME. The MSCs are prone to differentiate into tumour-associated fibroblasts upon signals from tumour secretome. Moreover, experimental data indicated that concomitant drug exposure of stromal cells together with tumour cells activated major alteration in signalling and secretome, which contributed to upregulation of cancer stem cell markers and increased drug resistance of tumour cells. We intend to test the evidence-guided measures how to prevent acquired drug resistance mediated by cell component in tumour stroma [Stem Cell Research 2012, 8:247-258; BMC Cancer 2013, 13:535; Thyroid 2014, 24:520-532; Cancer Microenvironment 2015, 8:1-14]

The Role of ALDH1 in Chemoresistance of Colon Cancer Cells (PI: Zuzana Kozovská)
There were several key stem cells markers identified in colon cancer: CD133, CD44, ALDH1, LGR5 and others. On the model of athymic mouse we observed the effect of molecular inhibition of ALDH1A1 in HT-29 cells by siRNA. We observed inhibition of proliferation of subcutaneous

xenografts in comparison to control cells in male mouse. Tumours induced by cells with inhibited ALDH1A1 grown faster in females [Biomedicine & Pharmacotherapy 2014, 68:911-916].

Hunting for the Dormant Cancer Cells (PI: Jozef Bízik)
Our results emphasize the potential role of activated stromal fibroblasts and subsequent inflammation in altering phenotype of plasma cells and directing myeloma progression towards dormancy. Given the significant implication of dormant myeloma cells that might serve as a major cellular basis for the relapse, understanding their unique biology and precise elucidation of the underlying molecular mechanisms for the maintenance of quiescence is highly important [Neoplasma 2012, 59:574-583; Neoplasma 2015, 62:938-948].

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)

Research output of the Institute consists of 75% of basic research and 25% of applied research.

Research output of the Institute consists of 95% of international research and 5% of national research.

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

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[42] SMOLKOVÁ, Božena - DUŠINSKÁ, Mária - HEMMINKI, Kari. NBN and XRCC3 genetic variants in childhood acute lymphoblastic leukaemia. In *Cancer epidemiology : The international journal of cancer epidemiology, detection and prevention*, 2014, vol. 38 no. 5, p. 563-568. (2.558 - IF2013). (2014 - Current Contents). ISSN 1877-7821.

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[44] SOROKINA, Svetlana - MARKOVÁ, Eva - GURSKÝ, Ján - DOBROVODSKÝ, Jozef - BELYAEV, Igor. Relative biological efficiency of protons at low and therapeutic doses in induction of 53BP1/[gama]H2AX foci in lymphocytes from umbilical cord blood. In *International Journal of Radiation Biology*, 2013, vol. 89, no. 9, p. 716-723. (1.895 - IF2012). (2013 - Current Contents). ISSN 0955-3002.

[45] ŠKORVAGA, Milan - NIKITINA, Ekaterina - KUBEŠ, Miroslav - KOŠÍK, Pavol - GAJDOŠECHOVÁ, Beata - LEITNEROVÁ, Michaela - COPÁKOVÁ, Lucia - BELYAEV, Igor. Incidence of common preleukemic gene fusions in umbilical cord blood in Slovak population. In *PLoS ONE*, 2014, vol. 9., iss. 3, p. e91116. (3.534 - IF2013). (2014 - MEDLINE). ISSN 1932-6203.

[46] TYČIAKOVÁ, Silvia - MATÚŠKOVÁ, Miroslava - BOHOVIČ, Roman - POLÁKOVÁ, Katarína - TORO, Lenka - ŠKOLEKOVÁ, Svetlana - KUČEROVÁ, Lucia. Genetically engineered mesenchymal stromal cells producing TNFα have tumour suppressing effect on human melanoma xenograft. In *The journal of gene medicine*, 2015, vol. 17, no. 1-2, p. 54-67. (2.472 - IF2014). (2015 - Current Contents). ISSN 1099-498X.

[47] VALOVIČOVÁ, Zuzana - MESÁROŠOVÁ, Monika - TRILECOVÁ, Lenka - HRUBÁ, Eva - MARVANOVÁ, Soňa - KRČMÁŘ, Pavel - MILCOVÁ, Alena - SCHMUCZEROVÁ, Jana - VONDRÁČEK, Jan - MACHALA, Miroslav - TOPINKA, Jan - GÁBELOVÁ, Alena. Genotoxicity of 7H-dibenzo[c,g]carbazole and its methyl derivatives in human keratinocytes. In *Mutation research-genetic toxicology and environmental mutagenesis*, 2012, vol. 743, no. 1-2, p. 91-98. (3.035 - IF2011). (2012 - Current Contents). ISSN 1383-5718.

[48] VASILYEV, Stanislav - KUBEŠ, Miroslav - MARKOVÁ, Eva - BELYAEV, Igor. DNA damage response in CD133+ stem/progenitor cells from umbilical cord blood: Low level of endogenous foci and high recruitment of 53BP1. In *International Journal of Radiation Biology*, 2013, vol. 89, no. 4, p. 301-309. (1.895 - IF2012). (2013 - Current Contents). ISSN 0955-3002.

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[50] **WARD, Thomas A. - *DUDÁŠOVÁ, Zuzana - SARKAR, Sovan - BHIDE, Mangesh R. - VLASÁKOVÁ, Danuša - CHOVANEC, Miroslav - MCHUGH, Peter J. Components of fanconi-like pathway control Pso2-independent DNA interstrand crosslink repair in yeast. In *PLOS Genetics : a peer-reviewed, open access journal*, 2012, vol. 8, no. 8, e1002884. (8.694 - IF2011). ISSN 1553-7390. Dostupné na internete: <http://www.plosgenetics.org/article/info%3Adoi%2F10.1371%2Fjournal.pgen.1002884>. doi:10.13.71/journal.pgen.1002884.*Zuzana Dudášová is considered as first author of the paper.**

2.1.3 List of monographs/books published abroad

AAA01 IARC WORKING GROUP ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS - ARMSTRONG, Bruce - BELYAEV, Igor - BLACKMAN, L.C.F - BLETTNER, Maria - CARDIS, Elisabeth - DASENBROCK, Clemens. *Non-ionizing radiation, part 2 : radiofrequency electromagnetic fields*. volume 102. Lyon, France : International agency for research on cancer, WHO press, 2013. ISBN 978 92 832 1325 3. ISSN 1017-1606.

2.1.4. List of monographs/books published in Slovakia

none

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

Chapters in scientific monographs published abroad

ABC01 ALTANER, Čestmír. Stem cell-mediated prodrug gene therapy of high-grade brain tumors : chapter 5. In *Stem cell therapeutics for cancer*. - New Jersey : Wiley-Blackwell, 2013, chapter 5, p. 59-73. ISBN 978-1-118-28242-7.

ABC02 BELYAEV, Igor. Biophysical mechanisms for nonthermal microwave effects. In *Electromagnetic fields in biology and medicine*. - New York : CRC Press : Taylor & Francis Group, 2015, p. 49 - 67. ISBN 978-1-4822-4850-0.

ABC03 BELYAEV, Igor. Electromagnetic field effects on cells and cancer risks from mobile communication. In *Bioelectromagnetic and subtle energy medicine*. 2nd edition. - Florida : CRC Press Taylor & Francis group, an infoma business, 2015, ch. 44, p. 517-538. ISBN 978-1-4822-3319-3.

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

none

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

none

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

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

Scientific publications	2012			2013			2014			2015			total			
	number	No. / FTE	No. / salary budget	number	No. / FTE	No. / salary budget	number	No. / FTE	No. / salary budget	number	No. / FTE	No. / salary budget	number	averaged number per year	av. No. / FTE	av. No. / salary budget
Scientific monographs and monographic studies in journals and proceedings published abroad *(AAA, ABA)*	0,0	0,000	0,000	1,0	0,016	0,001	0,0	0,000	0,000	0,0	0,000	0,000	**1,0**	**0,3**	**0,004**	**0,000**
Scientific monographs and monographic studies in journals and proceedings published in Slovakia *(AAB, ABB)*	0,0	0,000	0,000	0,0	0,000	0,000	0,0	0,000	0,000	0,0	0,000	0,000	**0,0**	**0,0**	**0,000**	**0,000**
Chapters in scientific monographs published abroad *(ABC)*	0,0	0,000	0,000	1,0	0,016	0,001	0,0	0,000	0,000	2,0	0,033	0,002	**3,0**	**0,8**	**0,012**	**0,001**
Chapters in scientific monographs published in Slovakia *(ABD)*	0,0	0,000	0,000	0,0	0,000	0,000	0,0	0,000	0,000	0,0	0,000	0,000	**0,0**	**0,0**	**0,000**	**0,000**
Scientific papers published in journals registered in Current Contents Connect *(ADCA, ADCB, ADDA, ADDB)*	34,0	0,556	0,042	28,0	0,448	0,035	27,0	0,420	0,034	31,0	0,519	0,036	**120,0**	**30,0**	**0,484**	**0,037**
Scientific papers published in journals registered in Web of Science Core Collection and SCOPUS *(ADMA, ADMB, ADNA, ADNB)*	6,0	0,098	0,007	2,0	0,032	0,002	5,0	0,078	0,006	6,0	0,100	0,007	**19,0**	**4,8**	**0,077**	**0,006**
Scientific papers published in other foreign journals (not listed above) *(ADEA, ADEB)*	2,0	0,033	0,002	2,0	0,032	0,002	2,0	0,031	0,003	0,0	0,000	0,000	**6,0**	**1,5**	**0,024**	**0,002**
Scientific papers published in other domestic journals (not listed above) *(ADFA, ADFB)*	2,0	0,033	0,002	4,0	0,064	0,005	0,0	0,000	0,000	5,0	0,084	0,006	**11,0**	**2,8**	**0,044**	**0,003**
Scientific papers published in foreign peer-reviewed proceedings *(AEC, AECA)*	0,0	0,000	0,000	0,0	0,000	0,000	1,0	0,016	0,001	0,0	0,000	0,000	**1,0**	**0,3**	**0,004**	**0,000**
Scientific papers published in domestic peer-reviewed proceedings *(AED, AEDA)*	5,0	0,082	0,006	4,0	0,064	0,005	10,0	0,155	0,013	0,0	0,000	0,000	**19,0**	**4,8**	**0,077**	**0,006**
Published papers (full text) from foreign and international scientific conferences *(AFA, AFC, AFBA, AFDA)*	0,0	0,000	0,000	0,0	0,000	0,000	3,0	0,047	0,004	0,0	0,000	0,000	**3,0**	**0,8**	**0,012**	**0,001**
Published papers (full text) from domestic scientific conferences *(AFB, AFD, AFBB, AFDB)*	2,0	0,033	0,002	0,0	0,000	0,000	0,0	0,000	0,000	7,0	0,117	0,008	**9,0**	**2,3**	**0,036**	**0,003**

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

In the chapter 2.1.2. only the publications with the leading role of the Institute were included (first or senior/corresponding author from the Institute). There were publications with high impact factor, where the Institute's researchers participated as co-authors and institutional address was included in the affiliations. These publications were excluded from the list of most important publications of the Institute and they are listed below:

ADCA01 ABRATE, Alberto - BUONO, Roberta - CANU, Tamara - ESPOSITO, Antonio - MASCHIO, Alessandro Del - LUCIANO, Roberta - BETTIGA, Arianna - COLCIAGO, Giorgia - GUAZZONI, Giorgio - BENIGNI, Fabio - HEDLUND, Petter - ALTANER, Čestmír - MONTORSI, Francesco - CAVARRETTA, Ilaria T.R. Mesenchymal stem cells expressing therapeutic genes induce autochthonous prostate tumour regression. In *European Journal of Cancer*, 2014, vol. 50, no. 14, p. 2478-2488. (4.819 - IF2013). (2014 - Current Contents). ISSN 0959-8049.

ADCA16 DAMMERMANN, Alexander - ČIPÁK, Ľuboš - GREGAN, Juraj. Microtubule organization: a pericentriolar material-like structure in yeast meiosis. In *Current Biology*, 2012, vol. 22, no. 7, p. R229-231. (9.647 - IF2011). (2012 - Current Contents). ISSN 0960-9822.

ADCA25 HEMMINKI, Kari - FRANK, Chritoph - FORSTI, Asta - MUSAK, Ludovit - KAZIMIROVA, Alena - BARANCOKOVA, Magdalena - HORSKA, Alexandra - VYMETALKOVA, Veronika - SMERHOVSKY, Zdenek - NACCARATI, Alessio - SOUCEK, Pavel - VODICKOVA, Ludmila - BUCHANCOVA, Janka - SMOLKOVÁ, Božena - DUŠINSKÁ, Mária - VODICKA, Pavel. Metabolic gene variants associated with chromosomal aberrations in healthy humans. In *Genes Chromosomes and Cancer : international journal*, 2015, vol. 54, no.4, p. 260-266. (4.041 - IF2014). (2015 - Current Contents). ISSN 1045-2257.

ADCA29 HYPPA, Randy W. - FOWLER, Kyle R. - ČIPÁK, Ľuboš - GREGAN, Juraj - SMITH, Gerald R. DNA intermediates of meiotic recombination in synchronous S. pombe at optimal temperature. In *Nucleic acids research*, 2014, vol. 42, no. 1, p. 359-369. (8.808 - IF2013). (2014 - Current Contents). ISSN 0305-1048.

ADCA30 CHAVDAROVA, Melita - MARINI, Victoria - SISAKOVA, Alexandra - SEDLACKOVA, Hana - VIGAŠOVÁ, Dana - BRILL, Steven J. - LISBY, Michael - KREJCI, Lumir. Srs2 promotes Mus81-Mms4-mediated resolution of recombination intermediates. In *Nucleic acids research*, 2015, vol. 43, no. 7, p. 3626-3642. (9.112 - IF2014). (2015 - Current Contents). ISSN 0305-1048.

ADCA35 KOVACIKOVA, Ines - POLAKOVA, Silvia - BENKO, Zsigmond - ČIPÁK, Ľuboš - ZHANG, Lijuan - RUMPF, Cornelia - MIADOKOVÁ, Eva - GREGAN, Juraj. A knockout screen for protein kinases required for the proper meiotic segregation of chromosomes in the fission yeast Schizosaccharomyces pombe. In *Cell Cycle*, 2013, vol. 12, no. 4, p. 618-624. (5.243 - IF2012). (2013 - Current Contents). ISSN 1538-4101.

ADCA45 LENČEŠOVÁ, Ľubomíra - HUDECOVÁ, Soňa - CSÁDEROVÁ, Lucia - MARKOVÁ, Jana - ŠOLTÝSOVÁ, Andrea - PASTOREK, Michal - SEDLÁK, Ján - WOOD, M.E. - WHITEMAN, Mathew - ONDRIAŠ, Karol - KRIŽANOVÁ, Oľga. Sulphide signalling potentiates apoptosis through the up-regulation of IP3 receptors types 1 and 2. In *Acta Physiologica : official journal of the Federation of European Physiological Societies*, 2013, vol. 208, no. 4, p. 350-361. (4.382 - IF2012). (2013 - Current Contents). ISSN 1748-1708. APVV-0045-11, VEGA 2/0074/13, CEMAN.

ADCA54 MEGO, Michal - ČIERNA, Zuzana - JANEGA, Pavol - KARABA, M. - MINÁRIK, G. - BENCAT, Jan - SEDLÁČKOVÁ, T. - SIEBEROVÁ, G. - GRONESOVÁ, Paulína - MANASOVÁ, D. - PINDAK, D. - ŠUFLIARSKY, Juraj - DANIHEL, Ľudovít - RUBEN, J.M. - MARDIAK, Jozef. Relationship between circulating tumor cells and epithelial to mesenchymal transition in early breast cancer. In *BMC Cancer*, 2015, vol. 15, no.533, p. 1-9. (3.362 - IF2014). (2015 - Current

Contents). ISSN 1471-2407. Dostupné na internete: <http://www.biomedcentral.com/1471-2407/15/533>.

ADCA58 MUHAMMAD, Abbas - CHAMPEIMONT, Jonathan - MAYR, Ulrike Beate - LUBITZ, Werner - KÚDELA, Pavol. Bacterial ghosts as carriers of protein subunit and DNA-encoded antigens for vaccine applications. In *Expert review of vaccines*, 2012, vol. 11, no. 1, p. 97-116. (4.251 - IF2011). (2012 - Current Contents). ISSN 1476-0584.

ADCA73 STRIOGA, Marius M. - FELZMANN, Thomas - POWELL JR., Daniel J. - OSTAPENKO, Valerijus - DOBROVOLSKIENE, Neringa T. - MATÚŠKOVÁ, Miroslava - MICHALEK, Jaroslav - SCHIJNS, Virgil. Therapeutic dendritic cell-based cancer vaccines: the state of the art. In *Critical Reviews in immunology*, 2013, vol. 33, no. 6, p. 489-547. (3.383 - IF2012). (2013 - Current Contents). ISSN 1040-8401.

ADCA74 TAKÁČOVÁ, Martina - BULLOVÁ, Petra - ŠIMKO, Veronika - ŠKVARKOVÁ, Lucia - POTURNAJOVÁ, M. - FEKETEOVÁ, L. - BABÁL, P. - KIVELA, A.J. - KUOPIO, T. - KOPÁČEK, Juraj - PASTOREK, Jaromír - PARKKILA, S. - PASTOREKOVÁ, Silvia.
Expression Pattern of Carbonic Anhydrase IX in MedullaryThyroid Carcinoma Supports a Role for RET-MediatedActivation of the HIF Pathway. In *American Journal of Pathology*, 2014, vol. 184, no.4, p. 953-965. (4.602 - IF2013). (2014 - Current Contents). ISSN 0002-9440.

ADCA75 TALEMI, Soheil Rastgou - KOLLÁROVIČ, Gabriel - LAPYTSKO, Anastasiya - SCHABER, Jorg. Development of a robust DNA damage model including persistent telomere-associated damage with application to secondary cancer risk assessment. In *Scientific Reports* [serial]. - Nature Publishing Group, 2015, vol. 5, ar.no. 13540, p. 1-13. (5.578 - IF2014). (2015 - Current Contents, Scopus, WOS). ISSN 2045-2322. Dostupné na internete: <http://www.nature.com/articles/srep13540>.

ADCA80 VODICKA, Pavel - MUSAK, Ludovit - FRANK, Christoph - KAŽIMÍROVÁ, Alena - VYMETALKOVÁ, Veronika - BARANČOKOVÁ, Magdaléna - SMOLKOVÁ, Božena - DZUPINKOVÁ, Zuzana - JIRASKOVA, Katerina - VODENKOVA, Sona - KROUPA, Michal - OSINA, Oto - NACCARATI, Alessio - PALITTI, Fabrizio - FORSTI, Asta - DUŠINSKÁ, Mária - VODICKOVÁ, Ludmila - HEMMINKI, Kari. Interactions of DNA repair gene variants modulate chromosomal aberrations in healthy subjects. In *Carcinogenesis*, 2015, vol. 36, no. 11, p. 1299-1306. (5.334 - IF2014). (2015 - Current Contents). ISSN 0143-3334.

ADCA82 ZHANG, Junfang - MARKUS, Ján - BIES, Juraj - PAUL, Thomas - WOLFF, Linda. Three murine leukemia virus integration regions within 100 kilobases upstream of c-myb are proximal to the 5' regulatory region of the gene through DNA looping. In *Journal of Virology*, 2012, vol. 86, no. 19, p. 10524-10532. (5.402 - IF2011). (2012 - Current Contents). ISSN 0022-538X.

ADMA11 PHADNIS, Naina - ČIPÁK, Ľuboš - POLÁKOVÁ, Silvia - HYPPA, Randy W. - ČIPÁKOVÁ, Ingrid - ANRATHER, Dorothea - KARVAIOVA, Lucia - MECHTLER, Karl - SMITH, Gerald R. - GREGAN, Juraj. Casein kinase 1 and phosphorylation of cohesin subunit rec11 (SA3) promote meiotic recombination through linear element formation. In *PLOS Genetics : a peer-reviewed, open access journal*, 2015, vol. 11, no. 5, e1005225. (7.528 - IF2014). ISSN 1553-7390. Dostupné na internete: <http://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1005225>.

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)	859,0	14,041	938,0	15,003	889,0	13,815	829,0	13,884	**3515,0**	**878,8**	**14,187**
Citations in SCOPUS (1.2, 2.2) if not listed above	123,0	2,010	172,0	2,751	160,0	2,486	167,0	2,797	**622,0**	**155,5**	**2,510**
Citations in other citation indexes and databases (not listed above) (3.2,4.2,9,10)	0,0	0,000	0,0	0,000	0,0	0,000	0,0	0,000	**0,0**	**0,0**	**0,000**
Other citations (not listed above) (3, 4, 3.1, 4.1)	19,0	0,311	15,0	0,240	4,0	0,062	9,0	0,151	**47,0**	**11,8**	**0,190**
Reviews (5,6)	0,0	0,000	0,0	0,000	0,0	0,000	0,0	0,000	**0,0**	**0,0**	**0,000**

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

KUČEROVÁ, Lucia - ALTANEROVÁ, Veronika - MATÚŠKOVÁ, Miroslava - TYČIAKOVÁ, Silvia - ALTANER, Čestmír. Adipose tissue-derived human mesenchymal stem cells mediated prodrug cancer gene therapy. In *Cancer Research*, 2007, vol. 67, no. 13, p. 6304-6313. (7.656 - IF2006). (2007 - Current Contents). ISSN 0008-5472.
VEGA 2/5028/26 CITATIONS 133

BROZMANOVÁ, Jela - MÁNIKOVÁ, Dominika - VLČKOVÁ, Viera - CHOVANEC, Miroslav. Selenium: a double-edged sword for defense and offence in cancer. In *Archives of Toxicology*, 2010, vol. 84, no. 12, p. 919-938. (3.312 - IF2009). (2010 - Current Contents). ISSN 0340-5761. **VEGA 2/6082/26 CITATIONS 98**

HORVÁTHOVÁ, Katarína - VACHÁLKOVÁ, Anna - OVESNÁ, Zdenka - TÓTHOVÁ, Darina. Pentacyclic triterpenoic acids: new chemoprotective compounds. In *Neoplasma*, 2004, vol. 51, no. 5, p. 327-333. (0.482 - IF2003). (2004 - Current Contents). ISSN 0028-2685.
VEGA no. 2/4005/04 CITATIONS 77

ALTANER, Čestmír. Prodrug cancer gene therapy. In *Cancer Letters*, 2008, vol. 270, no. 2, s. 191-201. ISSN 0304-3835. **Supported by grants from League against Cancer SR, SPP Foundation and FIDURA Capital Consult GmbH, Munich CITATIONS 76**

JAKUBÍKOVÁ, Jana - ADAMIA, Sophia - KOST-ALIMOVA, Maria - KLIPPEL, Steffen - CERVI, David - DALEY, John F. - CHOLUJOVÁ, Dana - KONG, Sun-Young - LEIBA, Merav - BLOTTA, Simona - OOI, Melissa - DELMORE, Jake - LAUBACH, Jacob - RICHARDSON, Paul G. - SEDLÁK, Ján - ANDERSON, Kenneth C. - MITSIADES, Constantine S. Lenalidomide targets clonogenic side population in multiple myeloma: pathophysiologic and clinical implications. In *Blood*, 2011, vol. 117, no. 17, p. 4409-4419. ISSN 0006-4971. **Slovak R&D Agency grant VVCE-0001-07 (J.S.) CITATIONS 69**

LETAVAYOVÁ, Lucia - VLČKOVÁ, Viera - BROZMANOVÁ, Jela. Selenium: From cancer prevention to DNA damage : review. In *Toxicology*. - Amsterdam : Elsevier, 2006, vol. 227, no. 1-2, p. 1-14. ISSN 0300-483X. **(VEGA no. 2/6082/26) CITATIONS 68**

KUČEROVÁ, Lucia - MATÚŠKOVÁ, Miroslava - HLUBINOVÁ, Kristína - ALTANEROVÁ, Veronika - ALTANER, Čestmír. Tumor cell behaviour modulation by mesenchymal stromal cells. In *Molecular cancer* [elektronický zdroj], 2010, vol. 9, article n. 129. (4.160 - IF2009). (2010 - Current Contents). ISSN 1476-4598. (**APVV-0260-07**, **VEGA 2/7060/27**). **CITATIONS 56**

ALTANER, Čestmír - ALTANEROVÁ, Veronika - BABINCOVÁ, Melánia - ČIČMANEC, Pavol - BABINEC, Peter. AC-magnetic field controlled drug release from magnetoliposomes: design of a method for site-specific chemotherapy. In *Bioelectrochemistry*, 2002, vol. 55, no. 1-2, p. 17-19. (2002 - Current Contents). **VEGA grant 1/8310/01 – projekt UK CITATIONS 48**

ALTANER, Čestmír. Glioblastoma and stem cells : minireview. In *Neoplasma*, 2008, vol. 55, no. 5, s. 369-374. (1.208 - IF2007). (2008 - Current Contents). ISSN 0028-2685 **The project is supported by grants from League Against Cancer SR, SPP Foundation and FIDURA Capital Con- sult GmbH, Munich CITATIONS 45**

CAVARRETTA, Ilaria T. - ALTANEROVÁ, Veronika - MATÚŠKOVÁ, Miroslava - KUČEROVÁ, Lucia - CULIG, Zoran - ALTANER, Čestmír. Adipose tissue-derived mesenchymal stem cells expressing prodrug-converting enzyme inhibit human prostate tumor growth. In *Molecular Therapy*, 2010, vol. 18, p. 223-231. (6.239 - IF2009). (2010 - Current Contents). ISSN 1525-0016. **(APVV-0260-07; financial support from SPP Foundation,**

FIDURA Capital Consult GmbH, Munich, Germany; and grant awarded by the League Against Cancer) CITATIONS 43

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

[1] Assoc. Prof. ALTANER Čestmír, D.Sc. 685 citations
[2] ALTANEROVÁ Veronika. Ph.D. 546 citations
[3] SEDLÁK Ján, D.Sc. 406 citations
[4] SLAMEŇOVÁ Darina, D.Sc. 368 citations
[5] KUČEROVÁ LUCIA, Ph.D. 342 citations

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

In the chapter 2.2.2. the publications with the leading role of the Institute were included only (first or senior/corresponding author from the Institute). There were some publications with more then 43 citations (selected top 10), where the Institute's researchers participated as co-authors and the Institute's address was included in the affiliations. These are listed below:

METIVIER, R. - GALLAIS, R. - TIFFOCHE, C. – LE PÉRON, C. - JURKOWSKA, R.Z. - CARMOUCHE, R.P. - IBBERSON, D. -BARÁTH, Peter - DEMAY, F.- REID, G. - BENES, V. - JELTSCH, A.- GANNON, F. - SALBERT, G. Cyclical DNA methylation of a transcriptionally active promoter. In *Nature*, 2008, vol. 452, no. 7183, p. 45-50. (28.751 - IF2007). (2008 - Current Contents, SCOPUS). ISSN 0028-0836. **CITATIONS 308**

WALSH, Tom - CASADEI, Silvia - COATS, Kathryn Hale – SWISHER, Elizabeth - STRAY, Sunday M. - HIGGINS, Jake - ROACH, Kevin C. - MANDELL, Jessica - LEE, Ming K. - ČIERNIKOVÁ, Soňa - FORETOVA, Lenka - SOUCEK, Pavel - KING, Mary-Claire. Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer. In *JAMA : the journal of the American Medical Association*, 2006, vol. 295, no. 12, p. 1379-1388. ISSN 0098-7484 **CITATIONS 125**

LETAŠIOVÁ, Silvia - JANTOVÁ, Soňa - ČIPÁK, Ľuboš - MÚČKOVÁ, Marta. Berberine-antiproliferative activity in vitro and induction of apoptosis/necrosis of the U937 and B16 cell. In *Cancer Letters*. - Elsevier Science Ireland, 2006, vol. 239, no. 2, p. 254-262. ISSN 0304-3835. **VEGA 1/1173/04, 2/4056/04 and APVT-51-019402 CITATIONS 52**

SANTOS, Janine Hertzog - MEYER, Joel N. - ŠKORVAGA, Milan - ANNAB, Lois A. - VAN HOUTEN, Bennett. Mitochondrial hTERT exacerbates free-radical-mediated mtDNA damage. In *Aging Cell*. - Oxford : Blackwell Pub., 2004, vol. 3, no. 6, p. 399-411. ISSN 1474-9718. **CITATIONS 44**

One of the most cited authors of the Institute in the evaluated period 2011-2014 left the Institute in 2010, so he is not on the list of the most cited authors - BARÁTH Peter, PhD. **392 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.

Most important research activities were identified by the Scientific Board of the CRI SAS every year based on the publications with the highest impact factors from the principal investigators of the Cancer Research Institute SAS.

1) Components of a Fanconi anemia-like pathway control Pso2-independent DNA interstrand crosslink repair in yeast

Fanconi anemia (FA) is a devasting genetic disease associated with defects in DNA interstrand cross-link (ICL) repair. The FA repair pathway is not thought to be conserved in *Saccharomyces cerevisiae*, and although the yeast Mph1 helicase is a putative homolog of human FANCM, yeast cells disrupted for *MPH1* are not sensitive to ICLs. We have revealed a key role for Mph1 in ICL repair when the Pso2 exonuclease is inactivated. We found that Mph1 physically and functionally interacts with Mgm101, mitochondrial genome maintenance factor, and the MutSα mismatch repair complex (Msh2-Msh6). Co-disruption of *MPH1*, *MGM101*, *MSH2*, or *MSH6* with *PSO2* produces an increase in ICL sensitivity, the elevation of ICL-induced chromosomal rearrangements, and persistence of ICL-associated DNA double-strand breaks. We also found that Mph1-Mgm101-MutSα directs the ICL-induced recruitment of Exo1 to chromatin. Hence, we proposed that Exo1 is an alternative 5'-3'exonuclease utilized for ICL repair in the absence of Pso2. Moreover, ICL-induced Rad51 chromatin loading is delayed when both Pso2 and components of the Mph1-Mgm101-MutSα and Exo1 pathway are inactivated, demonstrating that the homologous recombination stages of ICL repair are inhibited. Finally, the FANCJ- and FANCP-related factors Chl1 and Slx4, respectively, are also components of pathway controlled by Mph1-Mgm101-MutSα. Together, we suggest that a prototypical FA-related ICL repair pathway operates in budding yeast, which acts redundandly with the pathway controlled by Pso2, and is required for the targeting Exo1 to chromatin to execute ICL repair (Ward, Dudasova et al., PloS Genetics 2012, McHugh et al., Cell Cycle 2012).

Projects: Work was supported by the VEGA Grant Agency of the Slovak Republic (grant no. 2/0165/09) and by the project TRANSMED, part of the Research and Development Operational Programme funded by the European Regional Development Fund, European Social Fund – project code 13120200038.

2) Lif1 sumoylation and its role in non-homologous end-joining

DNA double-strand breaks (DSBs) are considered to be severe form of DNA damage. They can cause cell death if unrepaired, as well as promote processes leading to mutagenesis and tumorigenesis if misrepaired. Hence, effective DSB repair is crucial to maintain genome stability and cell viability. Two main mechanisms have evolved in cells to repair DSBs: nonhomologous end-joining (NHEJ) and homologous recombination. NHEJ repairs DSBs by tethering and ligating the broken DNA ends. In yeast, NHEJ requires Ku70-80 heterodimer, as well as the Mre11-Rad50-Xrs2 and Lif1-Nej1-Dnl4 complexes. While these components are quite well-characterized both in genetical and biochemical manner, the mechanisms regulating efficiency of NHEJ, as well as interplay between its components are not fully understood yet. We have identified and characterized the SUMOylation of the Lif1 protein, which is required for the ligation step in NHEJ. We showed that Lif1 SUMOylation occurs

throughout the cell cycle and requires the Siz1 and Siz2 SUMO ligases. We also revealed that single-stranded DNA (ssDNA), but not double-stranded DNA or the Lif1-interacting partner Nej1, is inhibitory to Lif1 SUMOylation. We identified lysine 301 as the major conjugation site and demonstrated that its replacement with arginine completely abolishes Lif1 SUMOylation in vivo and in vitro. The lif1-K301R cells exhibit increased levels of NHEJ compared to wild type cells throughout the cell cycle. This is likely due to inhibitory effect of SUMOylation on both Lif1 self-association and newly observed ssDNA binding activity. Our findings suggest that SUMOylation of Lif1 represents a new regulatory mechanism that downregulates NHEJ in a cell cycle phase-independent manner (Vigasova et al., Nucleic Acid Research. 2013)

Projects: APVV-0057-10, VEGA 2/0150/11.

3) Analysis of the role of protein kinases in regulation of fidelity of chromosome segregation

The complexity of genome maintenance is pointing out that this process is controlled by multi-level regulatory networks. Here, we studied the role of protein kinases in regulation of fidelity of chromosome segregation, focusing primarily on their involvement in regulation of essential steps of meiotic segregation, such as timely formation and removal of sister chromatid cohesion and crossing-over between homologs. We found that phosphorylation of cohesin subunits is required not only for segregation of sister chromatids, but is essential for high-level meiotic DNA breakage and recombination as well. Our results provide novel insights into the regulation of chromosomal features required for crossing-over and successful reproduction (Cipak et al., Nature Protocols, 2014, Phadnis et al., PLoS Genetics, 2015).

Projects: APVV-0111-12; VEGA 2/0014/14

4) Antitumor efficiency of prodrug-converting mesenchymal stromal cells

The efficacy of human adipose tissue-derived mesenchymal stromal cells (MSCs), engineered to express the suicide gene cytosine deaminase::uracilphosphoribosyltransferase was tested in several studies in combination with 5-fluorocytosine (5-FC) prodrug. On a pre-clinical model of intracranial rat glioblastoma it was demonstrated that prodrug-converting MSCs/5-FC retained tumor tropism and effectively inhibited glioblastoma growth. Continuous intracerebroventricular delivery of 5-FC using osmotic pump reduced the dose of prodrug required for the same therapeutic effect, and along with repeated administration of therapeutic stem cells increased the survival time (Altanerova et al., International Journal of Cancer 2012). Moreover, the same approach led to a long-term tumor free survival in melanoma xenograft bearing animals (Kucerova et al., Gene Therapy, 2014). Potent antitumor effect was demonstrated on these two aggressive hard-to-treat tumor models.

Projects: This work was supported by the Slovak Research and Development Agency under the contract No. APVV-0230-11 and APVV-0052-12, Scientific Grant Agency VEGA grant No. 2/0088/11 and 2/0171/13, the Cancer Research Foundation funding WAC2003, RFL2009 and RFL2012 and League against Cancer Foundation.

5) Intratumor heterogeneity

Solid tumors contain cell subpopulations with different properties with regard to tumorigenicity and chemosensitivity. Our study showed that the selected CD133+ subpopulation from medullary thyroid carcinoma was enriched for the chemoresistant tumor-initiating cells. These cells isolated from the drug-exposed xenografts, were significantly more resistant to 5-fluorouracil (5FU), which was associated with the substantial change in the expression profile of genes involved in 5FU metabolism and drug resistance. They retained chemoresistant properties upon culture propagation. These data suggested that the chemoresistant phenotype and the CD133+ MTC subpopulation emerged in response to chemotherapy in vivo (Kucerova et al., Thyroid 2014). Moreover, we also focused on the properties of stromal cells, which also significantly contribute to drug responses of tumors, They are non-malignant, however integral part of tumor microenvironment. Our data showed their specific behavior and responses upon gene transduction, tumor-dictated differentiation and and effect on tumor cells (Kucerova et al., Stem Cell Research 2012, Kucerova et al., BMC Cancer, 2013, Kucerova et al., Cancer Microenvironment, 2015).
Projects: This work was supported by the Slovak Research and Development Agency under the contract No. APVV-0230-11, APVV-0052-12, VEGA grants 2/0146/10, 2/0088/11, 2/0130/13 and 2/0171/13, funding from the Cancer Research Foundation RFL2009 and RFL2012.

6) Sustained induction of drug metabolizing enzymes in human hepatoma cells due to interactions between chemical carcinogens underlies the synergistic effects on DNA adduct formation

To gain a deeper insight into the potential interactions between individual aromatic hydrocarbons in a mixture, several benzo[a]pyrene (B[a]P) and 7H-dibenzo[c,g]carbazole (DBC) binary mixtures were studied in the HepG2 and WB-F344 liver cell lines. A lower frequency of micronuclei and levels of DNA adducts were found in rat liver WB-F344 cells treated with a binary mixture for 2h or 24h. The observed antagonism between B[a]P and DBC may be due to an inhibition of Cyp1a1 expression because cells exposed to B[a]P:DBC showed a decrease in Cyp1a1 mRNA levels. In human liver HepG2 cells exposed to binary mixtures for 2h, a reduction in micronuclei frequency was also found. However, after a 24h treatment, synergism between B[a]P and DBC was determined based on DNA adduct formation. Accordingly, the up-regulation of CYP1A1 expression was detected in HepG2 cells exposed to B[a]P:DBC. Our results show significant differences in the response of human and rat cells to B[a]P:DBC mixtures and stress the need to use multiple experimental systems when evaluating the potential risk of environmental pollutants. Our data also indicate that an increased expression of CYP1A1 results in a synergistic effect of B[a]P and DBC in human cells. As humans are exposed to a plethora of noxious chemicals, our results have important implications for human carcinogenesis (Gabelova et al., Toxicology and Applied Pharmacology, 2013).
Projects: The study was supported by VEGA grant 2/6063/27.

7) Role of NF1 in the expression of genes regulated by cellular stress

Oxidative stress and persistent activation of DNA damage response (DDR) are causally involved in the development of cellular senescence. Adenine nucleotide translocase-2 (ANT2) is consistently down-regulated in all three major forms of cellular senescence: replicative, oncogene-induced and drug-induced, in both normal and cancerous human cells.

We have shown formation of NF1/Smad transcription repressor complexes in senescent cells. Etoposide-induced formation of these complexes and repression of ANT2 were relatively late events co-incident with production and secretion of, and dependent on, TGF-β. TGF-β-mediated suppression of ANT2 through NF1/Smad4 complexes contributes to oxidative stress and DNA damage during induction of cellular senescence (Kretová et al., Cellular Signalling, 2014).

Projects: This study was supported by the Slovak Grant Agency VEGA 2/0107/11.

8) Effects of natural compounds on oxidant-induced DNA damage and antioxidant status

Men are daily exposed to different compounds present in the environment. In spite of advances in modern medicine which possess quantum of synthetic medicaments, many people prefer alternative medicine employing plant products. Positive effects of plants are attributed to the biologically active compounds which could reduce severe impacts of the environment, life style, eventually eliminate side effects of drugs. The biological effect of the plant extracts (Salvia officinalis, Thymus vulgaris, Lavandula angustifolia and Rosmarinus officinalis) has been studied on two types of liver cells - HepG2 cells and freshly isolated primary rat hepatocytes since the liver is the major site of xenobiotic metabolism and many liver diseases are associated with the oxidative stress. The main result of the project was the finding that plant extracts from Lamiaceae family possess great antioxidative potential. Protective effect of plant extracts has been detected also against DNA damaging effect of various genotoxins. Additionally, plant extracts influenced the activity of antioxidant enzyme GPx, as well as changed the activity of ERK that could be responsible for inhibition of proliferation of HepG2 cells (Kozics et al., Food Chemistry, 2013).

Projects: This work was supported from VEGA 2/0012/12, 2/0177/11, TRANSMED, ITMS: 26240120008 a TRANSMED 2, ITMS: 26240120030.

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

The Young Oncologists Competition
Date: March 6-7, 2012
Place: Cancer Research Institute, Bratislava, Slovakia
Scientific Committee: Soňa Čierniková, Beata Mladosievičová, Michal Mego, Július Brtko, Katarína Luciaková, Lucia Kučerová, Miroslav Chovanec, Slovakia

6th DNA Repair Workshop
Date: June 3-7, 2012
Place: Smolenice Castle, Smolenice, Slovakia
Local Organizing Committee: Miroslav Piršel, Slovakia, Miroslav Chovanec, Slovakia, Ján Gurský, Slovakia Dominika Mániková, Slovakia
Scientific Programme Committee: Miroslav Chovanec, Slovakia, Peter McHugh, Oxford, UK, Miroslav Piršel, Slovakia, Ben Van Houten, Pittsburgh, USA

2nd Natural Compounds in Cancer Prevention and Treatment
Date: October 1-4, 2012
Place: Smolenice Castle, Smolenice, Slovakia
Scientific and Organizing Committee: Ján Sedlak , Slovakia, Pavol Kúdela, Austria, Slovakia, Costas Ioannides, United Kingdom, Ľubica Hunáková, Slovakia, Paulína Gronesová, Slovakia, Clarissa Gerhaeuser, Germany, Vinjar Fonnebo, Norway, Jozef Duraj, Slovakia
Anupam Bishayee, USA

FEBS Workshop: Nucleotide excision repair and interstrand crosslink repair - from molecules to man
Date: June 9-13, 2013
Place: Smolenice Castle, Smolenice, Slovakia
Scientific Programme Committee: Caroline Kisker, Wuerzburg, Germany, Peter McHugh, Oxford, UK, Miroslav Piršel, Slovakia, Ben Van Houten, Pittsburgh, PA, USA
Local Organizing Committee:Miroslav Piršel, Slovakia, Miroslav Chovanec, Slovakia Ján Gurský, Slovakia, Dominika Mániková, Slovakia, Zuzana Šestáková, Slovakia

Genetic Toxicology and Cancer Prevention
Date: October 13-16, 2013
Place: Smolenice Castle, Smolenice, Slovakia
Scientific Programme Committee:
Alena Gábelová, Slovakia, Ivan Chalupa, Slovakia Hana Lehocká Czech Republic, Eva Miadoková, Slovakia, Darina Slameňová, Slovakia, Jan Topinka, Czech Republic

The Young Oncologists Competition
Date: March 6-7, 2014
Place: Cancer Research Institute, Bratislava, Slovakia
Scientific Committee: Soňa Čierniková, Michal Mego, Július Brtko, Zdena Sulová, Lucia Kučerová, Miroslav Chovanec, Slovakia

Genetic Toxicology and Cancer Prevention
Date: June 15-18, 2015
Place: Smolenice Castle, Smolenice, Slovakia
Scientific Programme Committee: Alena Gábelová, Slovakia, Július Brtko, Slovakia, Ivan Chalupa, Slovakia, Hana Lehocká, Czech Republic, Eva Miadoková, Slovakia, Jan Topinka, Czech Republic

2.3.3. List of edited proceedings from international scientific conferences.

[1] *6th DNA repair workshop: Book of Abstracts*. Bratislava: Ústav experimentálnej onkológie SAV, 2012 (DNA repair workshop).

[2] *Natural compounds in cancer prevention and treatment 2012: program and abstracts*. Bratislava: Ústav experimentálnej onkológie SAV, 2012. ISBN 978-80-970128-7-8 (Natural compounds in cancer prevention and treatment 2012).

[3] *Súťaž mladých onkológov pri príležitosti 6. Dňa výskumu rakoviny: zborník prednášok*. Margita Klobušická, Jela Brozmanová, Soňa Čierniková. Bratislava: Nadácia Výskum rakoviny, 2012. ISBN 978-80-970926-5-8 (Súťaž mladých onkológov 2012).

[4] *Genetic toxicology and cancer prevention: book of abstracts*. Alena Gábelová, Katarína Kozics. Bratislava : Cancer Research Institute of the Slovak academy of sciences, 2013. ISBN 978-80-970128-8-5 (Genetic toxicology and cancer prevention : Bilateral Czech and Slovak meeting).

[5] *FEBS DNA repair workshop: Book of abstracts*. Miroslav Piršel, Miroslav Chovanec, Ján Gurský, Dominika Mániková, Zuzana Šestáková. Brno : Tribun EU, 2013. ISBN 978-80-263-0383-1 (FEBS DNA repair workshop).

[6] *Súťaž mladých onkológov 2014: zborník prednášok*. Soňa Čierniková, Roman Bohovič, Margita Klobušická. Bratislava : Nadácia Výskum rakoviny : Ústav experimentálnej onkológie

SAV, 2014. 145 s. ISBN 978-80-971621-0-8 (Súťaž mladých onkológov 2014 : pri príležitosti 8. Dňa výskumu rakoviny).

[7] *Genetic toxicology and cancer prevention: book of abstracts*. Alena Gábelová, Monika Šramková. Bratislava : Cancer research institute of the Slovak academy of sciences, 2015. ISBN 978-80-970128-9-2 (Genetic toxicology and cancer prevention : Bilatelar Czech and Slovak meeting).

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)

Neoplasma (Published 6 times per year by AEPress, s.r.o. in English language)

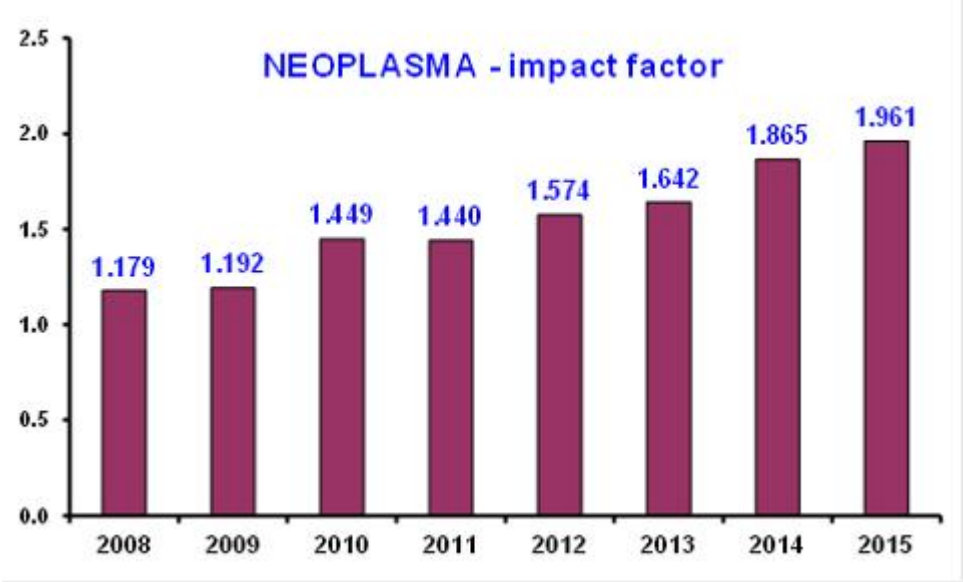
Abstracted and indexed in: PubMed http://www.ncbi.nlm.nih.gov/pubmed/,Current Contents (Life Sciences), Excerpta Medica database (EMBASE), Google Scholar (Index Copernicus), CrossRef (Digital Object Identifiers: DOI)

IF 2012: 1.574

IF 2013: 1.642

IF 2014: 1.865

IF 2015: 1.961



2.3.4.2. SCOPUS (none)

2.3.4.3. other databases (none)

2.3.4.4. not included in databases (none)

- **National position of the institute**

2.3.5. List of selected projects of national importance

The projects of the APVV and VEGA grant agencies as listed below.

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

(*10 selected projects coordinated by the CRI SAS*)

2012:

[1] DNA repair and preleukemic clones in cord blood stem cells, APVV-0669-10, 05/2011-10/2014, Assoc. Prof. Belyaev Igor, D.Sc.
[2] Identification of predictive epigenetic biomarkers in breast cancers, APVV-0076-10, 05/2011-05/2014, Fridrichová Ivana, PhD.

[3] Regulation of DNA double-strand repair mechanism choice, APVV-0057-10, 05/2011-04/2014, Chovanec Miroslav, PhD.

[4] Targeted Augmented Cellular Therapy against Tumor Initiating and Chemoresistant Cells, APVV-0230-11, 07/2012-12/2015, Kučerová Lucia, PhD.

[5] The role of bacteria in a process of carcinogenesis and syndrome of acquired immunodeficiency, APVV-06-46-11, 07/2012-12/2015, Assoc. Prof. Zajac Vladimír, PhD.

2013:

[6] Role of essential protein kinases in regulation of meiotic chromosome segregation, APVV-0111-12, 10/2013-09/2016, Čipák Ľuboš, PhD.

[7] Role of microenvironment and B-cell immunity in the spontaneous regression of MM patients undergoing hight dose therapy and autologous stem cell transplantation, APVV-0854-12, 10/2013-06/2017, Lakota Ján, MD., PhD.

[8] Mechanisms of interactions and bystander effect mediated by mesenchymal stromal cells expressing prodrugconverting genes on tumour stem cells, APVV-052-12, 10/2013-09/2017, Matúšková Miroslava, PhD.

2015:

[9] Study of repair of chemotherapy-induced DNA damage using Saccharomyces cerevisiae as a model system, APVV-14-0783, 07/2015 - 06/2018, Chovanec Miroslav, PhD.

[10] Prognostic biomarker for colorectal carcinoma based on miRNA analysis and characterization of selected proteins in the circadian context, APVV-14-0318, 07/2015-06/2019, Sedlák Ján, D.Sc.

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

Selected projects, mentioned in the chapter 2.3.1 that provided financial support for the most significant research outcomes of the basic research.

Project Leader	Project title, Project Number, Duration
Čipák Ľuboš, Ph.D.	**[1]** Role of protein kinases in regulation of chromosome segregation, 2/0014/14, 1.1.2014 / 31.12.2017
Fridrichová Ivana, Ph.D./ Krivulčík Tomáš, Ph.D.	**[2]** Histone modification and DNA methylation relationship in transcription silencing of cancer associated genes, 2/0120/13, 1.1.2013 / 31.12.2016
Hunáková Ľubica, Ph.D.	**[3]** Anticancer effects of isothiocyanates and their combination with other therapeutic approaches, 2/0177/11, 1.1.2011 / 31.12.2014
Kozics Katarína, Ph.D.	**[4]** Protective potential of plant extracts in experimental systems *in vitro* and *ex vivo, 2/0012/12, 1.1.2012 / 31.12.2015*
Kozovská Zuzana, Ph.D.	**[5]** Reversion of chemoresistance of human cancer stem cells, 2/0130/13, 1.1.2013 / 31.12.2016
Kučerová Lucia, Ph.D.	**[6]** Molecular mechanisms of tumor-driven mesenchymal stromal cells' differentiation, 2/0088/11, 1.1.2011 / 31.12.2014
Luciaková Katarína, D.Sc.	**[7]** Role of NF1 in the expression of genes regulated by cellular stress, 2/0107/11, 1.1.2011 / 31.12.2014
Matúšková Miroslava, Ph.D.	**[8]** Study of interactions between tumour cells and mesenchymal stem cells carrying suicide genes, 2/0146/10, 1.1.2010 / 31.12.2012
Matúšková Miroslava, Ph.D.	**[9]** Cytotoxic Effect of Engineered Mesenchymal Stromal Cells on Human Chemoresistant Tumour Cells and Cancer Stem Cells, 2/0171/13, 1.1.2013 / 31.12.2016
Škorvaga Milan, Ph.D.	**[10]** Studies of molecular details in repair of clinically relevant DNA lesions, 2/0150/11, 1.1.2011 / 31.12.2014

2.3.8. Projects of SAS Centres of Excellence

[1] Center of excellence for the study of metabolic aspects of development, diagnostics and treatment of cancer diseases. 06/2011 – 12/2014, Sedlák Ján, D.Sc. – partner

2.3.9. National projects supported by EU Structural Funds

[1] Implementation of radiobiological research of intensity-modulated proton therapy into clinical oncology practice, ITMS: 262 202 201 29, 10/2010-03/2014, C / Assoc. Prof. Belyaev Igor, D.Sc.

[2] Centre of Excellence on Translational Research in Molecular (TRANSMED 2), ITMS: 262 401 200 30, 01/2010 - 12/2012, W / Sedlák Ján, D.Sc.

[3] Establishment of the Competence Centre for Research and Development in the Field of Molecular Medicine, ITMS: 26240220071, 06/2011-09/2014, W / Sedlák Ján, D.Sc.

[4] Diagnostics of socially important disorders in Slovakia, based on modern biotechnologies (DNA-DG), ITMS: 26240220058, 11/2010-10/2013, W / Fridrichová Ivana, Ph.D.

[5] University scientific park for biomedicine Bratislava, ITMS:262 402 200 87, 03/2013-07/2015, W / Sedlák Ján, D.Sc.

2.3.10. List of journals (published only in the Slovak language) edited/published by the institute: (none)

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

2.3.10.2. SCOPUS

2.3.10.3. Other databases

2.3.10.4. Not included in databases

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

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

BELYAEV, Igor. Role of physical and biological variables in bioeffects of non-thermal microwaves. The second Monte Veritá workshop: It is foundation for research on information technologies in society Zurich, Switzerland, 2012.

BELYAEV, Igor. DNA repair foci in cancer risk assessment, diagnostics and treatment. In *6th DNA repair workshop,* Smolenice, Slovakia, 2012.

BELYAEV, Igor. Effects of electromagnetic fields on DNA and risk of cancer. In *The 7th international EMF seminar in China*. Beijing, China: Academy of military medical sciences institute of radiation medicine, 2013.

BELYAEV, Igor. Electrohypersensitivity: input of mechanistic studies with low-intensity radiofrequency and extremely low frequency electromagnetic fields. 5th Paris Appeal Congress – Brussels, Belgium, 2015.

ĎURINÍKOVÁ, Erika. Chemoresistant colon cancer cells exhibit less sensitivity to treatment by mesenchymal stromal cells expressing prodrug-converting genes. *Forum of Italian researchers on mesenchymal and stromal stem cells* – Milano, Italy 2013.

FRIDRICHOVÁ, Ivana. DNA methylation profiles in advanced breast cancer. World congress on breast cancer – Birmingham, UK, 2015.

GÁBELOVÁ, Alena. Mechanisms of toxicity of tissue specific dibenzocarbazoles. *EEMGS 2015: European environmental mutagenesis and genomics society*. 44th Annual Meeting – Praha, Czech Republic, 2015.

KUČEROVÁ, Lucia. Cell-mediated enzyme/prodrug gene therapy in cancer. *2nd ICCTI workshop: recombinant vaccines, cellular vaccines and delivery systems* – Znojmo, Czech Republic, 2012.

KUČEROVÁ, Lucia. Tumor-driven changes in human mesenchymal stromal cells can generate phenotype of carcinoma-associated fibroblasts. *V4 international conference analytical cytometry VII*, Mikulov, Czech Republic, 2013.

KUČEROVÁ, Lucia. Tumor microenvironment: cross talk between tumor and mesenchymal stromal cells. *18th Joint meeting: Signal transduction receptors, mediators and genes* – Signal transduction society STS, Weimar, Germany, 2014.

MARKOVÁ, Eva. Response of human hematopoietic stem cells and lymphocytes from umbilical cord blood to [gama]-radiation and protons at low and therapeutical doses. *Contribution of epigenetic mechanisms that influence susceptibility to radiation-induced cancer* - Centre for Radiation Protection Research Stockholm University, Stockholm, Sweden 2013.

SEDLÁK, Ján. The effect of MGN-3 arabinoxylan on innate imunity cells. *BITs 6th Annual World Cancer Congress (WCC-2013): Theme: a New Era in Cancer Research and Therapy* - Venue: XI an, China, 2013.

ŠESTÁKOVÁ, Zuzana. DNA repair helicase - the story with an unexpected end. In XVIIth *Gliwice scientific meetings,* Gliwice, Poland 2013.

VASILYEV, Stanislav. DNA damage response in CD133+ stem/progenitor cells from umbilical cord blood: high recruitment of 53BP1 and γH2AX pan-staining. *6th DNA repair workshop,* Smolenice, Slovakia, 2012.

VIGAŠOVÁ, Dana. SUMO regulates the ligation step of NHEJ. *6th DNA repair workshop* Smolenice, Slovakia, 2012.

ZAJAC, Vladimír. What is the role of bacteria in AIDS?, World Congress on Virology, Las Vegas, USA, 2012.

ZAJAC, Vladimír. Microbes in AIDS. International conferece on HIV/AIDS, STDs, and STIs: 151st OMICS group conference). Orlando-FL, USA, 2013.

ZAJAC, Vladimír. The study of bacteria and yeasts in HIV-positive patients. World congress on Virology, Baltimore, USA, 2013.

ZAJAC, Vladimír. Intestinal and respiratory tract bacteria and yeasts in pathogenesis of aids. In *4th World Congress on Virology,* San Antonio, 2014.

ZAJAC, Vladimír. The role of human microbiome in AIDS process. In OMICS International Organises. *5th World Congress on Virology,* Atlanta, USA, 2015.

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

Assoc. Prof. Altaner Čestmír, D.Sc. – chairman Session 3: Treating Acute Myeloid Leukemia tomorrow (Program and Organizing Committee), XXVI Symposium IACRLRD, Torino, 2013

Assoc. Prof. Belyaev Igor, D.Sc. – chairman of the Program and Organizing Committee of The 7th International EMF Seminar, Beijing, China, 2013

Chovanec Miroslav, Ph.D. – member of the Program and Organizing Committee of the 6th DNA Repair Workshop, Smolenice, 2012

Gábelová Alena, Ph.D. – member of the Program Committee of the 44th Annual Meeting of European Environmental Mutagenesis and Genomics Society, Prague, 2015

Horváthová Eva, Ph.D. – member of the Organizing Committee of the conference 19th Interdisciplinary Toxicological Conference TOXCON 2014 "Connecting for Safer Europe", Stará Lesná, 2014

Horváthová Eva, Ph.D. – member of the Organizing Committee of the conference 17th Interdisciplinary Toxicology Conference TOXCON 2012 "Toxicology at the Crossroad", Stará Lesná, 2012

Piršel Miroslav, Ph.D. – member of the Program Committee of the 6th DNA Repair Workshop, Smolenice, 2012

Piršel Miroslav, Ph.D. – chairman of the Organizing Committee of the 6th DNA Repair Workshop, Smolenice, 2012

Piršel Miroslav, Ph.D. – chairman of the Organizing Committee of the FEBS Workshop, Smolenice, 2013

Piršel Miroslav, Ph.D. – member of the Program Committee of the FEBS Workshop, Smolenice, 2013

- **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

ĎURINÍKOVÁ, Erika. Pokroky v modernej génovej terapii [Modern advances in gene therapy]. *6. celoslovenská konferencia zdravotníckych pracovníkov pracujúcich v mamológii*. - Bratislava, Slovakia, 2014.

KUČEROVÁ, Lucia. Hierarchia nádorových buniek a nádorové kmeňové bunky [The hierarchy of tumor cells and tumor stem cells]. *19. medzinárodná pracovná konferencia SEKCAMA*. - Bratislava, Slovakia, 2014.

KUČEROVÁ, Lucia. Metastázovanie: epitelovo-mezenchýmových prechod [Metastasis: epithelial-mesenchymal transition]. *6. celoslovenská konferencia zdravotníckych pracovníkov pracujúcich v mamológii*. - Bratislava, Slovakia, 2014.

KUČEROVÁ, Lucia. Vplyv nádorového mikroprostredia na chemorezistenciu nádorových buniek [Effect of tumor microenvironment on tumor cells chemoresistance]. *XXI. Biologické dny. Pokroky a výzvy současné nádorové biologie*. Brno, Czech Republic, 2014.

KUČEROVÁ, Lucia. Engineered MSC as prodrug activators in antitumor treatment. *XI. Diagnostic, predictive and experimental oncology days : abstract book*. - Olomouc, Czech Republic, 2015.

MATÚŠKOVÁ, Miroslava. MSC and Cancer - Two Sides of One Coin. *Stem cells and cell therapy: From research to modern clinical application,* Černá Hora, Czech Republic, 2013.

MATÚŠKOVÁ, Miroslava. Interactions of therapeutic MSC with colon cancer cells in 3D conditions. *Stem cells and cell therapy: From research to modern clinical application* Černá Hora, Czech Republic, 2014.

SEDLÁK, Ján. Regulácia signálnych dráh v cirkadiánnom kontexte [Regulation of signaling pathways in the context of the circadian]. *Dni molekulovej patológie : 11. sympózium molekulovej patológie s medzinárodnou účasťou a Martinské dni nelekárskych pracovníkov v patológii*. - Bratislava , Slovakia, 2015.

ŠKOLEKOVÁ, Svetlana. Mechanizmy ovplyvnenia chemorezistencie nádorových buniek v nádorovom mikroprostredí [The mechanisms affecting chemoresistance of cancer cells in the tumor microenvironment]. *19. medzinárodná pracovná konferencia SEKCAMA*. - Bratislava , Slovakia, 2014.

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

Gábelová Alena, PhD - chairman of the Program Committee of the conference Genetic Toxicology and Cancer Prevention, Smolenice, 2013

Gábelová Alena, PhD – scientific supervisor of the conference Genetická toxikologie a prevence rakoviny (Program and Organizing Committe), Brno, 2014

Gábelová Alena, PhD - chairman of the Program Committee of the conference Genetic Toxicology and Cancer Prevention, Smolenice, 2015

Gronesova Paulina, PhD - member of the Program and Organizing Committee of the 2nd conference Natural Compounds in Cancer Prevention and Treatment, Smolenice, 2012

Hunáková Ľubica, PhD - member of the Program and Organizing Committee of the 2nd conference Natural Compounds in Cancer Prevention and Treatment, Smolenice, 2012

Chalupa Ivan, PhD **-** member of the Program Committee of the conference Genetic toxicology and cancer prevention, Smolenice, 2013

Kozics Katarína, PhD - member of the Organizing Committee of the conference Genetic Toxicology and Cancer Prevention, Smolenice, 2015

Kučerová Lucia, PhD - member of the Program Committee of the conference 19. medzinárodná pracovná konferencia SEKCAMA, Bratislava, 2014

Kučerová Lucia, PhD – member of the Program Committee (Scientific Committee) of the conference XI. Diagnostic, Predictive and Experimental Oncology Days, Olomouc, 2015

Kretová Miroslava, PhD - member of the Organizing Committee of the conference Genetic Toxicology and Cancer Prevention, Smolenice, 2015

Kretová Miroslava, PhD - member of the Organizing Committee of the conference Genetic Toxicology and Cancer Prevention, Smolenice, 2013

Luciaková Katarína, PhD - member of the Organizing Committee of the conference Genetic Toxicology and Cancer Prevention, Smolenice, 2013

Sedlák Ján, DSc - member of the Program and Organizing Committee of the 2nd conference Natural Compounds in Cancer Prevention and Treatment, Smolenice, 2012

Sedlák Ján, DSc – member of the Program Committee of the conference Bratislavské onkologické dni, XLIX. ročník, Bratislava, 2012

Sedlák Ján, DSc – member of the Program Committee of the conference Bratislavské onkologické dni, L. ročník, Bratislava, 2013

Sedlák Ján, DSc – member of the Program Committee of the conference Bratislavské onkologické dni, LI. ročník, Bratislava, 2014

Sedlák Ján, DSc – member of the Program Committee of the conference Bratislavské onkologické dni, LII. ročník, Bratislava, 2015

Šramková Monika, PhD - member of the Organizing Committee of the conference Genetic Toxicology and Cancer Prevention, Smolenice, 2015

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

The national status of the Institute is reflected by its long historical continuity as the Institute was established in 1946. In Slovakia, the Institute has a unique position as an academic institution pursuing basic oncological and translational research with long-term continuity. During the assessed period 2012-2015, the research at the CRI SAS was focused on understanding of the basic mechanisms of cancer and development of novel therapeutic strategies for the disease. It is obvious from the summary of R & D activities, that some topics are stably incorporated with long-lasting continuity and tradition (molecular mechanisms of DNA repair pathways, mesenchymal stem cells, chemical carcinogenesis and genetic toxicology, antitumor signalling pathways triggered by natural compounds), but there are several perspective research directions which have been initiated recently (nanomaterials for therapeutic applications, Nano:Bio interactions and biosafety, cancer biomarkers, radiobiology and cancer risk assessment, tumour microenvironment, intratumour heterogeneity and cancer stem cells). This is reflected in increasing possibilities and invitations for collaboration on multilateral grant applications. Our scientists are also invited to give lectures as invited speakers at national and international conferences.

We hosted some excellent speakers at the Institute as well:
Igor Jurisica, PhD., Ontario Cancer Institute, IBM Life Sciences Discovery Center, Toronto, Canada
Mária Dušinská, PhD., NILU – Norwegian Institute for Air Research, Kjeller, Norway
Prof. Miri Cohen, PhD., Department of Gerontology, University of Haifa, Haifa, Israel
Prof. Tariq Enver, Cancer Institute, University College London, United Kingdom
Petra Hammerlik, PhD., Danish Cancer Society Research Centre, Kopenhagen, Denmark
Prof. Peter J. McHugh, Department of Oncology, University College Oxford, Oxford, United Kingdom

The attractiveness of the research topics is also reflected in the interest of university students to apply for our undergraduate and PhD. programs.

In the international context, the CRI SAS is a member of the prestigious Organisation of European Cancer Institutes and collaborates with a large number of outstanding national, European and US laboratories. The CRI SAS is a member of the DNA Repair Network and the Comet Assay Network. The scientists from the CRI are members of various international societies (EACR, FEBS, EEMS, WHO, ASMB), Editorial Boards of the international scientific journals, Scientific Committees at scientific meetings, or Scientific Evaluation Committees. Presentation at numerous international conferences gives support for the significance of the research at CRI SAS. PhD and post-doctoral students have been awarded travel grants and scholarships to attend scientific meetings or to stay in outstanding laboratories abroad.

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

- **International projects and funding**

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

	Project title	Typ / Project number	Duration in months	Funding for the Institute (EUR)	Role of the Institute / Responsible person
2012	Arsenic in cancer treatment: mechanism of action and new forms of delivery	SAS-NSC JRP 2010/03	01/2011-12/2013	16 650 EUR (2012) 16 551 EUR (2013)	C / Sedlák Ján, D.Sc.
2013	Cancer diagnostics and assessment of cancer risk	MAD	01/2013-12/2015	684 EUR (2013) 684 EUR (2014) 0 EUR (2015)	C / Assoc. Prof. Beliaev Igor, D.Sc.
	Individual radiosensitivity of cancer patients and nuclear-chemical personnel	MAD	01/2013-12/2015	684 EUR (2013) 684 EUR (2014) 0 EUR (2015)	C / Marková Eva, PhD.
2014	none				
2015	none				

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

Centers of Excellence

Center of excellence for the study of metabolic aspects of development, diagnostics and treatment of cancer diseases. 06/2011 – 12/2014, Sedlák Ján, D.Sc. – partner, funding for the institute 22 500,-EUR

SASPRO:

Functional consequences of renal cell activation due to iron oxide and gold nanoparticle uptake. 0084/01/02, 08/2015 – 07/2018, Bábelová Andrea, Ph.D., funding for the institute 201 224,- EUR
Identification of substrates of essential protein kinases using shokat mutants. 0032/01/02, 04/2015 – 03/2018, Čipák Ľuboš, Ph.D., funding for the institute 222 978,- EUR
Clonal dynamics of multiple myeloma. 0064/01/02, 09/2015 – 08/2018, Jakubíková Jana, Ph.D., funding for the institute 208 307,- EUR

Environmental Health Trust, USA

In vitro research on RF-EMF induced DNA alterations in three cell types. 08.2011 - 12/2012, Assoc. Prof. Belyaev Igor, D.Sc. – partner, funding for the institute 25 000,- EUR

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

1. The impact of surface chemistry of superparamagnetic iron oxide nanoparticles on nano.bio interactions in vitro. NILU-TAF-258, 01/2015 – 02/2015, Norway, Buliaková Barbora, M.Sc.
2. The mutagenic and carcinogenic activity of surface modified superparamagnetic iron oxide nanoparticles in vitroce modified iron oxide nanoparticles. NILU-TAF-320, 01/2015 – 02/2015,

Norway, Gábelová Alena, Ph.D.

3. Study of Global DNA Methylation in Epithelial-Mesenchymal Transition Processes at Single Cell Level. Effect of Gold Nanoparticles on DNA Methylation. NILU-TAF-279, 07/2014 – 08/2014, Norway, Smolková Božena, Ph.D.
4. Protective effect of plant extracts from Salvia officinalis and Thymus vulgaris against silver nanoparticles induced DNA damage in human hepatoma HepG2 cells. NILU-TAF-333, 01/2015 – 02/2015, Norway, Srančíková Annamária, M.Sc.

- **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	Typ / Project number	Duration in months	Funding for the Institute (EUR)	Role of the Institute / Responsible person
2012	DNA repair and preleukemic clones in cord blood stem cells	APVV-0669-10	05/2011-10/2014	72 252 EUR (2012) 49 785 EUR (2013) 33 323 EUR (2014)	C / Assoc. Prof. Belyaev Igor, D.Sc.
	Neurobiology of cancer: the study of the nervous system role in etiopathogenesis of tumor growth and development of metastasis	APVV-0007-10	05/2011-10/2014	15 984 EUR (2012) 16 734 EUR (2013) 12 290 EUR (2014)	I / Bízik Jozef, D.Sc.
	Identification of predictive epigenetic biomarkers in breast cancers	APVV-0076-10	05/2011-05/2014	57 271 EUR (2012) 54 495 EUR (2013) 15 009 EUR (2014)	C / Fridrichová Ivana, Ph.D.
	Antitumour effect of biologically active ligands of nuclear retinoid X receptor heterodimers in tissue carcinoma cell lines?	APVV-0160-11	07/2012-12/2015	4 565 EUR (2012) 9 122 EUR (2013) 8 118 EUR (2014) 10 126 EUR (2015)	I / Hunáková Ľubica, Ph.D.
	Hypericin: biotechnology, signalome, photodynamic therapy	APVV-0040-10	05/2011-10/2014	2 185 EUR (2012) 2 223 EUR (2013) 1 105 EUR (2014)	I / Chalupa Ivan, Ph.D.
	Regulation of DNA double-strand repair mechanism choice	APVV-0057-10	05/2011-04/2014	77 146 EUR (2012) 76 328 EUR (2013) 22 568 EUR (2014)	C / Chovanec Miroslav, Ph.D.
	Identification of biomarkers associated with treatment resistance in testicular germ cell tumors	APVV-0016-11	07/2012-12/2015	8 616 EUR (2012) 17 045 EUR (2013) 15 276 EUR (2014) 15 551 EUR (2015)	I / Chovanec Miroslav, Ph.D.
	Targeted Augmented Cellular Therapy against Tumor Initiating and Chemoresistant Cells	APVV-0230-11	07/2012-12/2015	24 406 EUR (2012) 37 963 EUR (2013) 31 894 EUR (2014) 39 412 EUR (2015)	C / Kučerová Lucia, Ph.D.
	The role of bacteria in a process of carcinogenesis and syndrome of acquired immunodeficiency	APVV-06-46-11	07/2012-12/2015	10 033 EUR (2012) 32 471 EUR (2013) 29 902 EUR (2014)	C / Assoc. Prof. Zajac Vladimír, Ph.D.
2013	Role of essential protein kinases in regulation of meiotic chromosome segregation	APVV-0111-12	10/2013-09/2016	14 200 EUR (2013) 40 757 EUR (2014) 42 332 EUR (2015)	C / Čipák Ľuboš, Ph.D.
	Chemoenzymatic synthesis and evaluation of biological activities of natural glycophenolics and their analogues	APVV-0846-12	10/2013-09/2017	4 405 EUR (2013) 11 223 EUR (2014) 16 207 EUR (2015)	I / Duraj Jozef, Ph.D.

	Role of microenvironment and B-cell immunity in the spontaneous regression of MM patients undergoing hight dose therapy and autologous stem cell transplantation	APVV-0854-12	10/2013-06/2017	14 262 EUR (2013) 48 104 EUR (2014) 61 035 EUR (2015)	C / Lakota Ján, M.D., Ph.D.
	Mechanisms of interactions and bystander effect mediated by mesenchymal stromal cells expressing prodrug converting genes on tumour stem cells	APVV-0052-12	10/2013-09/2017	10 148 EUR (2013) 37 579 EUR (2014) 47 237 EUR (2015)	C / Matúšková Miroslava, Ph.D.
2014	none				
2015	Development of novel diagnostic method for clinical oncology based on the interaction of DNA aptamers with proteins	APVV-14-0267	07/2015-06/2019	5 013 EUR (2015)	I / Bízik Jozef, D.Sc.
	Elucidation of novel pro-metastatic functions of tumor-associated carbonic anhydrase IX and its cross-talk with pro-inflammatory response	APVV-14-0816	07/2015-06/2019	7 490 EUR (2015)	I / Bízik Jozef, D.Sc.
	Study of repair of chemotherapy-induced DNA damage using Saccharomyces cerevisiae as a model system	APVV-14-0783	07/2015 - 06/2018	32 573 EUR (2015)	C / Chovanec Miroslav, Ph.D.
	Prognostic biomarker for colorectal carcinoma based on miRNA analysis and characterization of selected proteins in the circadian context	APVV-14-0318	07/2015-06/2019	13 866 EUR (2015)	C / Sedlák Ján, D.Sc.

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	16	18	20	20
Funding in the year (EUR)	108 565	125 126	138 066	118 076

- **Summary of funding from external resources**

2.4.6. List of projects supported by EU Structural Funds

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	Implementation of radiobiological research of intensity-modulated proton therapy into clinical oncology practice	ITMS: 262 202 201 29	10/2010-03/2014	438 531,00 (2012) 17 274,32 (2013) 128 892,61 (2014) 38 981,41 (2015)	C / Assoc. Prof. Belyaev Igor, D.Sc.
	Centre of Excellence on Translational Research in Molecular (TRANSMED 2)	ITMS: 262 401 200 30	01/2010 - 12/2012	6 749,93 (2012)	W / Sedlák Ján, D.Sc.
	Establishment of the Competence Centre for Research and Development in the Field of Molecular Medicine	ITMS: 262 402 200 71	06/2011-09/2014	30 290,22 (2013) 70 254,17 (2014)	W / Sedlák Ján, D.Sc.
	Diagnostics of socially important disorders in Slovakia, based on modern biotechnologies (DNA-DG)	ITMS: 262 402 200 58	11/2010-10/2013	9 920,39 (2012) 10 307,22 (2013) 6 369,60 (2014)	W / Fridrichová Ivana, Ph.D.
2013	University scientific park for biomedicine Bratislava	ITMS:262 402 200 87	03/2013-07/2015	9 151,89 (2015)	W / Sedlák Ján, D.Sc.
2014	none				
2015	none				

External resources	2012	2013	2014	2015	total	average
External resources (milions of EUR)	0,455	0,058	0,206	0,048	**0,767**	**0,192**
External resources transfered to coooperating research institute (milions of EUR)	0,000	0,000	0,000	0,000	**0,000**	**0,000**

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

In the assessed period we were able to get other financial support from several funding bodies for our research activities.

Slovak Cancer Research Foundation - Slovakia

BMP-4 mediated differentiation of the cancer stem cell as a first step towards suicide gene therapy in glioblastoma. NVR 2014-2015, Cihová Marína, PhD.

Chemoresistance abrogation in human cancer stem cells by inhibition of ALDH1A1 enzyme. NVR1, 07/2012 -06/2013, Matúšková Miroslava, PhD.

League against Cancer Foundation – Slovakia

Isolation of human mesenchymal stem cells and their use in regenerative and gene therapy. 01/2006 – 12/2012, Assoc. Prof. Altaner Čestmír, D.Sc.

Human mesenchymal stem cells and their use in regenerative therapy and gene therapy for cancer. 01/2006 – 12/2015 Assoc. Prof. Altaner Čestmír, D.Sc.

Ján Korec Foundation - Slovakia

Genetic analysis of inhabitants coming from Zlatniky and Male Hoste. 01/2011 – 01/2012, Poturnajová Martina, PhD.

Projects funded by the Private Sphere (FIDURA Capital Consult GmbH)

Isolation of human mesenchymal stem cells and their use in regenerative and gene therapy. 01/2006 – 12/2012 (FIDURA Capital Consult GmbH), Assoc. Prof. Altaner Čestmír, D.Sc.

Nanoparticles in cancer gene therapy and labeling of human stem cells with magnetic fluid and their follow up by MRI, 01/2008 – 12/2012 (FIDURA Capital Investment Ltd. Mnichov), Altanerová Veronika, Ph.D.

Projects funded by the Private Sphere (NOVARTIS) –awarded for the best young investigator

Financial support for the exploitation of the adult stem cell in the glioblastoma treatment, 2013-2014, Cihová Marína, PhD.

2.5. PhD studies and educational activities

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

The Cancer Research Institute BMC SAS is actively involved in the education and training of the undergraduate students (Master thesis) and graduate students (Rigorous Thesis) mainly from the Comenius University (Faculty of Genetics, Anthropology, Medicine and Molecular Biology), and the Slovak Technical University. Moreover, the Institute is accredited for teaching Ph.D. students in two accredited Ph.D. scientific education programs:
[1] Experimental Oncology 7.1.15 (15-14-9) – Medical Faculty, Comenius University, validity: indefinite period of time
[2] Genetics 4.2.4 (15-03-9) – Faculty of Natural Sciences, Comenius University, validity: to the upcoming complex accreditation of University (year 2015)
[3] ERASMUS programme - cooperation with Department of Microbiology and Virology, Comenius University

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

PhD study	31.12.2012			31.12.2013			31.12.2014			31.12.2015		
Number of potential PhD supervisors	26			27			27			29		
PhD students	number	defended thesis	students quitted	number	defended thesis	students quitted	number	defended thesis	students quitted	number	defended thesis	students quitted
Internal	15,0	5,0	0,0	17,0	1,0	0,0	14,0	4,0	0,0	14,0	1,0	0,0
External	0,0	0,0	0,0	0,0	0,0	0,0	3,0	0,0	0,0	3,0	0,0	0,0
Other supervised by the research employees of the institute	2,0	0,0	0,0	3,0	0,0	0,0	3,0	1,0	0,0	2,0	1,0	0,0

Several foreign PhD students received training during their stay at the CRI SAS:

Raquel Rubio, MSc., Institution: University of Philippines, Date: 11. – 15.5.2015

Iren Elisabeth Sturtzel, Institution: Norwegian Institute for Air Research NILU, Project: Project Qnano, SMU-TAF-492: Possible immunomodulatory and epigenetic effects of nanofibrillar cellulose.

Date: 12.6.2015-26.6.2015

Naouale El Yamani, PhD., Institution: Norwegian Institute for Air Research NILU Project: Project Qnano, SMU-TAF-490: Assessment of DNA methylation changes induced by AgNPs exposure by two independent methods, methylation-sensitive comet assay and pyrosequencing, Date: 23.1.2015-02.2 2015

Svetlana Sorokina, PhD., Institution: Institute of Theoretical and Experimental Biophysics, Russian Academy of Science, Russia, Pushchino, Project: The National Scholarship Programme of the Slovak Republic. Date: 01.02.2011-30.09.2011

Serazhutdin A. Abdullaev, PhD., Institution: Institute of Theoretical and Experimental Biophysics, Russian Academy of Science, Russia, Pushchino, Project: The National Scholarship Programme of the Slovak Republic. Date: 01.02.2011-31.11.2011

Ekaterina Nikitina, PhD., Institution: Cancer Research Centre, Siberian Branch of the Russian Academy of Medical Sciences, Tomsk, Russia, Project: The National Scholarship Programme of the Slovak Republic. Date: 01.02.2012-30.09.2012 Project: SAS-RAMS project "Cancer diagnostics and accessibility of cancer risks". Date: 02.06.2013-14.06.2013 and 01.10.2014-15.10.2014

Stanislav Vasiliev, PhD., Institution: Institute of Medical Genetics, Siberian Branch of the Russian Academy of Medical Sciences, Tomsk, Russia, Project: SAS-RAMS project "Individual radiosensitivity of cancer patients during radiation therapy and nuclear-chemical personnel". Date: 30.09.2014-13.10.2014

2.5.3. Summary table on educational activities

Teaching	2012	2013	2014	2015
Lectures (hours/year)[2]	28	25	32	20
Practicum courses (hours/year)[2]	6	6	67	30
Supervised bachelor theses (in total)	0	1	3	4
Supervised diploma theses (in total)	21	12	10	22
Supervised PhD theses (in total)	17	20	20	19
Members in PhD committees (in total)	3	6	5	4
Members in DrSc. committees (in total)	0	0	1	1
Members in university/faculty councils (in total)	2	2	2	2
Members in habilitation/inauguration committees (in total)	1	2	1	1

1

Addition:
In total, 1830 hours spent with Diploma students in the year 2012
In total, 598 hours spent with Diploma students in the year 2013
In total, 118 hours spent with Diploma students in the year 2014
In total, 562 hours spent with Diploma students in the year 2015

2.5.4. List of published university textbooks

[0]

2.5.5. Number of published academic course books

[0]

2.5.6. List of joint research laboratories/facilities with universities

[0]

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

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

Our PhD students applied for the grants to visit the international laboratories and gather experience. ***Svetlana Školeková, MSc.*** received Erasmus grant from Comenius University in Bratislava, Faculty of Medicine for The expenses during intership at the Institute of Molecular and Translational Medicine, Olomouc, Czech Republic, September – november 2015.

Lenka Toro, MSc. received financial support from the National grant programme of Academic mobility, SAIA, n.o., to visit Universidad de Antioquia (UdeA), Facultad de Odontologia, Medellin, Colombia, 2015-2016 (6 months).

The CRI BMC SAS has signed contract for cooperation with following subjects:

Medical Faculty of Comenius University, Bratislava: in the field of pregraduate and postgraduate programs and in the area of participation on the common research-and- development projects with the aim to achieve the corresponding degree in scientific and practical experience of the students in the study program 7.1.15 Oncology. The aim is to functionally interconnect basic and clinically-oriented research with the teaching activities in the field of Oncology and increase the efficiency of the collaboration of the joined research groups on particular projects.

Institute of Pathological Anatomy and Institute of Medical Biology, Genetics and Clinical Genetics: the cooperation is mostly executed in the form of student education to increase their interest in the molecular biology and clinical genetics. Students are also encouraged, consulted and take part in student conferences and Diploma thesis. Assoc prof. V. Zajac has given regularly lectures for the students at the Institute of Pathological Anatomy. The scientists from the CRI BMC SAS are members of the committee in the PhD study program 7.1.15 Oncology and 7.1.21 Pathological Anatomy and Forensic Medicine. Moreover, the scientists were members of the commitee at Medical Sciences Student Conference and Scientific Conference of PhD students, Medical Faculty of Comenius University.

Faculty of Natural Sciences, Comenius University, Bratislava: in the field of pregraduate and postgraduate programs and in the area of participation on the common research-and-development projects with the aim to achieve the corresponding degree in scientific and practical experience of the students in the study program 4.2.4 Genetics.

Department of Genetics: collaboration is in the field of DNA repair in yeast S. cerevisiae. The research subject is the major topic for diploma thesis, which are realized in the laboratory and the experimental data are the subject of consultation. Another line of cooperation covers the research in the genotoxicology and it is realized in the form of diploma thesis, publications in research journals and presentations within the scientific conferences.
Department of Anthropology: The scientists of the Department of Genetics CRI BMC SAS cooperate in study program 4.2.8 Anthropology by the participation of its members in Diploma and PhD thesis Committee and the involvement of the diploma students in research grant.

Faculty of Pharmacy, Comenius University, Bratislava
Department of Cellular and Molecular Biology of Drugs: The cooperation lies within the supervision of Diploma thesis of undergraduate students in the field of oncology and study of the effect of chemotherapy on the growth and properties of cancer stem cells. In the frame of the collaboration, these students participated on the ongoing research projects of the department of Oncology CRI BMC SAS. The outcomes are regularly presented in the form of publications in scientific journals and presentations at international conferences and students conferences.

Faculty of Science, Pavol Jozef Šafárik University, Košice.
Institute of Biology and Ecology: The cooperation was launched by the same interest in the application of flow cytometric technologies in the analysis of heterogeneous cell mixtures. Cooperation was manifested by common project in the frame of Center of Excellence funded by Slovak R&D Agency 2008-2011. Subsequently, the study programme Cytoanalytics was created at

the Faculty of Science and experts from our Institute serve as members of programme committee in university studies in the master and doctoral levels.

Faculty of Chemical and Food Technology, Slovak Technical University, Bratislava
Department of Biochemistry and Microbiology: The cooperation lies within the supervision of diploma thesis of undergraduate student in the field of genotoxicology and the effect of natural compounds on cell signaling circuits. In the frame of collaboration, these students are expected to visit the experimental laboratory and gather some practical experience in the various methodologies in the field of genetic toxicology research. The outcomes are regularly presented in the form of publications in scientific journals and presentations at international conferences.

Slovak Medical University, Bratislava
HIV/AIDS Reference Centre: Collaboration lies within the evaluation of the role of intestinal bacterial flora in acquired immunodeficiency syndrome. This expectation is based on our data which detected HIV-like sequences in the bacteria and their specific intracellularization properties. These properties make them real candidates for potential horizontal gene transfer between procaryotic and eucaryotic system.

Faculty of Medicine, Department of Clinical and Experimental Genetics as well as Department of Immunology and Immunotoxicology: The scientists of Department of Genetics of the CRI BMC SAS collaborated with the members of these departments as co-authors of several high-impact publications according to their former collaboration on the research grants.

Institute for Cardiovascular Physiology, Goethe-University, Frankfurt am Main: The cooperation is based on supervising Medical Physiology Seminar for undergraduated medical students. Thanks to this cooperation there is a possibility to perform certain experiments in the laboratories of the Institute and to use equipment not available in the BMC SAS, as well as scientific exchange of the methodology and novel techniques running in the Institute.

Based on the long-standing cooperation between the CRI BMC SAS and the Slovak Cancer Research Foundation (SCRF), SCFR has funded the project NaDia to support professional growth and increase in practical skill of the PhD. students. The financial support for the specific material increases the scope of the novel infrastructure exploitation.

2.6. Social impact

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

Most important results of applied and translational research projects were identified by the Scientific Board of the CRI SAS every year based on the publications with highest impact factors by principal investigators from the Cancer Research Institute SAS.

1) Aberrant DNA methylation and protein expression profiles associated with invasiveness and metastasis processes in breast cancers

In our breast cancer studies we found the association between increasing *RASSF1A* methylation levels and tumour size, metastatic lymph node status and higher TNM stage together with strong relation between less frequent, but high level of *CDH1* methylation and metastatic lymph nodes. The other original result was the positive correlation between *RASSF1A* methylation levels and percentage of cancer cells expressing oestrogen and progesterone receptor that could be useful for the prognosis of hormonal therapy response. Furthermore, we showed that the risk for lymph node metastases development and higher proliferation of cancer cells measured through Ki-67 expression was increased by hypermethylation of *CXCL12* and *ADAM23* genes, respectively. Our results indicate that quantification of *CDH1, CXCL12* and *ADAM23* methylation levels could be useful markers for monitoring of metastatic potential in breast cancers. In breast tumour tissues, no relationship between DNA methylation levels in 11 genes and expressions of relevant proteins was observed; however, the positive CXCL12 protein expression and lack of SOCS1 protein expression were associated with the presence of circulating tumour cells in the circulation of patients that indicate the aberrant signalling cross-talk between cytokine and chemokine responses in haematogenous dissemination of cancer (Kajabova et al, Translational Oncology, 2013, Fridrichova et al., Translational Research, 2015).
Projects: Slovak Research and Development Agency (APVV) under the contract No. APVV-0076-10, Research and Development Operational Programme (ERDF), contract No.26240220058 and Scientific Grant Agency (VEGA), contracts No. 2/0065/10, 2/0120/13, 2/0169/14, 1/0724/11 and 2/0092/15, funding from the Cancer Research Foundation RFL2010.

2) **Simulation of clinical scenario of antitumor therapy with therapeutic mesenchymal stromal cells**

Glioblastoma multiforme (GBM) is the most deadly brain cancer. GBM with current treatment modalities is incurative. The therapeutic efficacy of human mesenchymal stem cells derived from bone marrow and from adipose tissue, engineered to express the suicide gene cytosine deaminase::uracil phosphoribosyltransferase was evaluated to treat intracerebral rat C6 glioblastoma in a simulated clinical therapeutic scenario. Intracerebrally grown glioblastoma was treated by resection and subsequently with single or repeated intracerebral inoculations of therapeutic stem cells followed by a continuous intracerebroventricular delivery of 5-fluorocytosine using an osmotic pump. We observed curative therapy of glioblastoma by therapeutic cell-mediated prodrug gene therapy caused by the destruction of both tumor cells and the niche where glioblastoma initiating cells resided (Altaner et al., International Journal of Cancer 2014).
Metastatic spread of tumor cells remains a serious problem in cancer treatment, which is extremely difficult in triple-negative breast cancer (TNBC). We demonstrated curative effect on experimental metastases derived from TNBC achieved by synergistic action of mesenchymal stromal cells expressing yeast cytosine deaminase::uracil phosphoribosyltransferase (CD::UPRT) and with Herpes simplex virus thymidine kinase (HSVtk) in the presence of prodrugs 5-fluorocytosin (5-FC) and ganciclovir (GCV). Systemic administration of CD::UPRT-MSC and HSVtk-MSC in combination with 5-FC and GCV inhibited growth of MDA-MB-231 induced lung metastases. Combined gene-directed enzyme/prodrug therapy mediated by MSC exerted synergic cytotoxic effect and resulted in

high therapeutic efficacy in vivo (Matuskova et al., J Exp Clin Cancer Res. 2015). Different type of therapuetic MSCs was used to control metastatic melanoma growth and the results have shown significant antitumor effect (Tyciakova, Journal of Gene Medicine, 2015).
Projects: This work was supported by the Slovak Research and Development Agency under the contracts No. APVV-0052-12 and APVV-0230-11, by VEGA grants No. 2/0171/13 (M.M.), 2/0088/11 (L.K.), 2/0087/15 (L.K.) and 2/0130/13 (Z.K.), by the NADIA, RFL2009 and WAC2003 programs funded by the Slovak Cancer Research Foundation and by TRANSMED2, ITMS: 26240120030 supported by the Research & Development Operational Programme funded by ERDF, and foundation League against Cancer.

3) **Novel gene-directed enzyme/prodrug therapy (GDEPT) for medullary thyroid carcinoma**

The extent of local bystander effect induced by fusion yeast cytosine deaminase::uracil phosphoribosyltransferase (yCD) in combination with 5-fluorocytosine (5FC) was evaluated in xenogeneic model of human medullary thyroid carcinoma (MTC). This approach to gene-directed enzyme/prodrug therapy (GDEPT) induces strong bystander cytotoxicity. Effector yCD-TT mixed with target EGFP-TT cells in a ratio 2:9 could achieve significant tumor regression and 14-fold decrease in serum marker calcitonin upon 5FC administration. Histopathological analysis unraveled that antitumor effect resulted in tumor dormancy and proliferation arrest of remaining tumor cell clusters in vivo. yCD/5FC combination represents another GDEPT approach to achieve tumor growth control in MTC (Kucerova et al., Cancer Letters, 2013).
Projects: Study was supported by the Slovak Research and Development Agency under the contract No. APVV-0230-11, the VEGA Grants Nos. 2/0088/11 (L.K.) and 2/0146/10 (M.M.).

4) **Incidence of common preleukemic fusion genes in umbilical cord blood in Slovak population.**

Umbilical cord blood mononuclear cells obtained from 500 Slovak newborns were analyzed for the presence of prognostically important preleukemic fusion genes (PFG) by real-time quantitative PCR with sensitivity 1-3 x 10-5. The screening revealed a relatively high incidence of these PFG, namely 2.4% TEL-AML1, 5% BCR-ABL (p190), and 0.8% MLL-AF4. The corresponding fusion transcripts achieved very low level, usually less than 6 copies per 100,000 cells. We assume that most of these PFG may originate relatively late in fetal development and will be probably eliminated during postnatal development. Analysis of cell populations with leukemogenic potential should provide a better diagnostic and prognostic tool and help prevent donor cell-derived leukemia (Skorvaga et al., PLoS ONE, 2014).
Projects: The Slovak Research and Development Agency (APVV 0669-10), The National Scholarship Program of the Slovak Republic (SAIA), The Joint Research Project “Cancer diagnostics and assessment of cancer risks” between Slovak Academy of Sciences (SAS) and Russian Academy of Medical Sciences (RAMS), The VEGA Grant Agency (2/0150/11)

5) Genetic analysis of novel RET gene mutation in two villages with high occurence of thyroid neoplasia

The population study of residents coming from 2 joined villages near Topoľčany has confirmed higher occurrence of thyroid neoplasia there. Genetic testing of inherited RET gene mutations revealed that seven (4,8%) unrelated individuals of 147 tested individuals bear RET Ala641Ser as a sole mutation in same area. Based on negative medical findings data in 6 patients with p.Ala641Ser alone, it can be local polymorphism found in isolated area as a result of founder effect and consanguinity. Based on transforming properties Ala641Ser can be still considered as RET mutation Class A with very low transforming potential, so lifetime monitoring of patients is recommended. We analyzed the self-association of RET transmembrane domains carrying germline mutations p.Ala641Ser and p.Ser649Leu compared to wild-type. Our results indicate that the p.Ala641Ser mutation has no significant

effect on the self-association activity of RET transmembrane domain. Interestingly, the p.Ser649Leu mutation causes a dramatic decrease of RET transmembrane domain self-association, indicating a novel, yet unknown mechanism of c-RET proto-oncogene activation (Benej et al., Neoplasma 2013).
Projects: Foundation of Ján Korec, VEGA 2/0091/08.

6) **Identification of aberrant erythroid development in acute erythroid leukemia or myelodysplastic syndrome**

In-depth multiparameter fow cytometry immunophenotyping of nucleated erythroid progenitors during bone marrow regeneration revealed that the expression of CD105 and CD117 is critical for the distinction between 4 phenotypically different developmental stages of nucleated erythroid progenitors: pro-erythroblasts, basophilic erythroblasts, polychromatophilic erythroblasts and orthochromatophilic erythroblasts. CD105 antigen expression was specifically associated with pro-erythroblasts and basophilic erythroblasts, whereas CD117 was expressed at the earliest pro-erythroblast stage (Fajtova et al., Leukemia and Lymphoma 2013).
Projects: VEGA 2/0041/10, 2/0134/13 a NFM/EEA SK0095

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

The researchers of the Cancer Research Institute organized conference entitled „The importance of the research for the tertiary prevention“ linked to the roundtable discussion on the occasion of the Day Against Cancer on March 5th, 2015. Participants formulated essential needs of the scientific research in oncology including, but not limited to these:

- Reinitiate the National Oncology Registry in Slovakia
- Ensure solving multidisciplinary oncology projects within the frame of the governmentally driven-health programe(s) based on the priorities in health system and call for the integrated projects of research and development in Slovakia
- Establish interconnected tumor tissue banks in the key centers of clinical oncology as a prerequisite for the realization and evaluation of the research and preventive programs
- Ensure stable and predictable financial support for the established grant agencies with rigorous peer-review process in Slovakia and stabilize financial support in mid-term horizon exceeding the functional period of the government
- Create conditions for the open access to the scientific results which were achieved with the financial support from the public sources and governmental support for everybody in the society to be able to access them
- Implement preventive and therapeutic national oncology program based on the up-to date knowledge from the international summits and scientific conferences in Europe and in the world

The critical issues for the cancer research were formulated and signed by all participants of the discussion. The memorandum entitled “It’s not beyond us” was delivered to the Ministry of Health of the Slovak Republic and discussed with the major representatives to incorporate these issues into the health priorities for Slovakia. Memorandum is available on the website and can be signed by public supporters as well.
Symposium Integrative oncology held on November 2015 in Martin supported the campaign “It’s not beyond us” and contributed to the activity “Open House”. The participants agreed with the memorandum and stressed the need for the financial support of the multidisciplinary oncological projects with significant role of all the key players in oncology including oncology clinics, research institutes and patient organizations.

Dr. Alena Gabelova was involved in FP7-ERANET-2010-RTD, ERA-NET on Translational Cancer Research as a Steering Commitee Member (national representative) and Scientific Manager in 2011-2014.

2.6.3. List of contracts and research projects with industrial and other commercial partners, incl. revenues (none)

2.6.4. List of licences sold abroad and in Slovakia, incl. revenues (none)

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

Since 1993, when the Slovak Cancer Research Foundation (SCRF) was established, it (co)-organized in close cooperation with the researchers from the Cancer Research Institute (CRI) BMC SAS many fund-raising campaigns which enabled to get unique scientific devices and improve infrastructure for the oncology research. Moreover, CRI scientists together with the SCRF organized several scientific workshops, conferences and public activities with the aim to promote the goals and results of basic as well as translational cancer research. Educational and preventive intention was achieved by cooperation of the CRI scientists with the SCRF via **Scientific Workshops – Oncology** (http://vdo.sav.sk/) and **The Young Oncologists Competition** (http://www.nvr.sk/aktivity-a-podujatia/de-vyskumu-rakoviny/su-az-mladych-onkologov-2012/, http://www.nvr.sk/aktivity-a-podujatia/de-vyskumu-rakoviny/sutaz-mladych-onkologov-2/).

Fund-raising campaigns promoting the importance of cancer research in public over the years 2012-2015:

RUN FOR LIFE

In collaboration with the TESCO foundation, there was a campaign “Run for Life”, which was organized in 6 cities all around Slovakia with the aim to reach 14.000 participants and collect 85.000€ for purchasing the scientific device INCUCYTE in 2012. (Bratislava on May 5th, Prešov on May 12th, Žilina on May 19th, Nitra on May 26th, Trenčín on June 9th, Banská Bystrica on June 16th, 2012). This campaign was focused on a general public to spread the idea of the cancer research support by joining the run, which was an important reminder of one way how to prevent cancer and other diseases linked to limited physical activity.

The same project was launched also in 2013 with the aim to reach 15.000 participants in 6 Slovak cities and collect 90.000 EUR for the device NanoSight. (Bratislava on May 4, Banská Bystrica on May 11, Prešov on May 18, Nitra on May 25, Žilina on June 8, Trenčín on June 15). Both campaigns were successful and the Slovak Cancer Research Foundation could provide both devices to the Institute researchers for their experiments.

SKATING FOR HOPE

CRI researchers have been active in assisting during the project “Skating for Hope". This activity took place on February 2nd, 2015, and was initiated as a social and charitable sporting event with donation to the Slovak Cancer Research Foundation. The aim was to offer participants an attractive sporting activity in winter time with a varied cultural program and raise money for purchaising of experimental and diagnostic equipments for cancer research. But especially, to emphasize the role of physical activity in prevention of cancer and knowledge that each form of help in fighting against cancer can bring the benefit for cancer patients.

ON THE WHEELS AGAINST CANCER

The researchers of the Institute also took part, actively helped to organize and promote ideas of public annual campaign and donation “On the Wheels against Cancer”. This campaign, co-organized by the SCRF and the Slovak Paralympic Committee, started its journey in 2003 under the auspices of Paralympic winner from Sydney 2000 in cycling sprint Radovan Kaufman, who died of cancer at the age of 25. The campaign motto was “You can join us!” and people were encouraged

to join by many ways: wearing a badge “Jazdím proti rakovine” (Driving against Cancer) to express the support, organize their own event of driving against cancer on any vehicle with wheels – roller skates, bicycles, scooters, and thus support the aims of the campaign. Public events started in 2003 were organized annually in May in Bratislava, in June in Partizánske, in August in Smolenice and in September in Košice and Žilina.

2.6.6. Summary of relevant activities, max. 300 words

The scientists of the Institute are fully aware of their responsibility to spread the knowledge and newest information toward the public, but also to communicate with the decision-making sphere in order to define the needs of all the people involved. This was very nicely demonstrated in logo of the campaign „Not beyond us“ showing the closed circle involving individual-society-government and patient-scientist-doctor.Therefore we have participated on the meeting with the representatives of the Ministry of Health and Ministry of Education to discuss the actual problems in a general perspective and research in particular.

We spread the annual highligths of the World Cancer Day very actively and mediate the information in many ways – mostly informal activities in a very tight collaboration with the Slovak Cancer Research Foundation.

Each year on February 4th, on the World Cancer Day, WHO and the International Agency for Research on Cancer (IARC) support the Union for International Cancer Control (UICC) to promote ways to ease the global burden of cancer. "Together it is possible" was the 2012 theme, reinforcing that it is only by every person, organization, and government individually doing their part that the world will be able to reduce premature deaths from cancer and other noncommunicable (chronic) diseases (NCD). Preventing cancer, improving treatment and raising quality of life for cancer patients as recurring themes were the subject of the World Cancer Day 2013. 1.5 million premature cancer deaths could be prevented per year if targets set to reduce NCDs by 25% are met by 2025. World Cancer Day 2014 with its campaign “Debunk the myths!” was targeted at public misunderstandings about cancer disease. World Cancer Day on February 4th, 2015, taking place under the tagline ‘Not beyond us’ took a positive and proactive approach to the fight against cancer, highlighting that solutions do exist across the continuum of cancer, and that they are within our reach. These ideas must be followed also in our society to ease the socio-economic burden of cancer diagnosis in society.

2.7. Popularisation of Science (outreach activities)

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

[1] Organization of “Open House” at the Cancer Research Institute
[2] Organization of the press conferences
[3] Publishing articles in press media and internet
[4] Appearances in telecommunication media
[5] Preparing public popularization lectures (SAVinci)
[6] Participation at the popular science event European Researchers´Night supported by the European Commision
[7] Participation at the fund-raising campaigns organized by the Slovak Cancer Research Foundation (Run for Life, Fighting Cancer on Wheels)
[8] Co-organization with SCRF the project “Scientific Workshop Oncology”
[9] Co-organization with SCRF the Young Oncologists Competition
[10] Co-organization with SCRF several scientific undertakings at the Cancer Research Day (March 7)
[11] Participation at SLOVMEDICA - 15th International Exhibition of Health Service, September 26-28, 2013

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	6	1	2	9	18
Appearances in telecommunication media popularising results of science, in particular those achieved by the Institute	6	5	0	9	20
Public popularisation lectures	19	183	134	119	455

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

We understand that the relationship between scientists and public is very important for opening the spaces for perceiving science and its impact on society. Popularization of science is especially important for cancer research as the need for compliance in preventive measures is high. Therefore, the scientists from the CRI SAS actively contribute to organization and regularly participate in activities organized by the Slovak Cancer Research Foundation. Next to raising funds from public donations and supporters, they increase the public information on the modern trends in cancer research. Oncology Workshop project with its focus on young people (aged 15-19) contributes to appreciation of the involvement of each one of us in the prevention of cancer. Projects like Run for Life or On the Wheels against Cancer draw public attention to significance of cancer research. Young scientists with an interest in oncology research are encouraged by our scientists to take part in the competition organized biannually to reward the best presentations, which helps to find dedicated students. Competing students have an opportunity to build their competence in the area of molecular biology, genetics and epigenetics, and other cancer research frontier fields, and interestingly, some of them indeed intend to follow up the research career. Each year, scientists prepare practical demonstrations aimed at students, teachers and publics within the research facility to illustrate some basic research techniques and visiting experimental laboratories allow them to see real research site in operation. In line with this, scientists regularly prepare information for the press releases on popularization activities providing the opportunity for non-scientists to get an insight into the academic field and medical research focused on cancer, its developments and activities to inform the non-scientific community about the relevant results of the field supporting better understanding of new solutions to health issues of the population.

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

2.8.1. Summary table of personnel

Personnel	2012	2013	2014	2015
All personnel	103,0	119,0	107,0	105,0
Research employees from Tab. Research staff	77,0	76,0	75,0	76,0
FTE from Tab. Research staff	46,180	45,520	50,350	45,710
Average age of research employees with university degree	46,5	46,5	46,7	46,3

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.								1	2
II.a / Assoc. prof.		1	8	2	3		2	2	1
Other researchers PhD./CSc.	3	9	5						
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.							3		1
II.a / Assoc. prof.		1		1	1	2	1	2	3
Other researchers PhD./CSc.	1		1						
doc. / Assoc. prof.							1		2

2.8.2. Postdoctoral and mobility scheme

2.8.2.1. Postdoctoral positions supported by national and international resources

Project Qnano, SMU-TAF-492: Possible ummunomodulatory and epigenetics effects of nanofibrillar cellulose: Iren Elisabeth Sturtzel (12.6.2015-26.6.2015)

Project Qnano, SMU-TAF-490: Assessment of DNA methylation changes induced by AgNPs exposure by two independent methods, methylation-sensitive comet assay and pyrosequencing: Naouale El Yamani, PhD. (23.1.2016-02.2.2015)

APVV-0669-10 „DNA repair and preleukemic clones in cord blood stem cells“: Charlotta Böiers, PhD. (18.03.2015-20.03.2015)

SAS-RAMS project „Cancer diagnostics and accessibility of cancer risks“: Ekaterina Nikitina, PhD (02.06.2013-14.06.2013, 01.10.2014-15.10.2014)

SAS-RAMS project „Individual radiosensitivity of cancer patients during radiation therapy and nuclear-chemical personnel“: Stanislav Vasiliev, PhD. (30.09.2014-13.10.2014)

2.8.2.2. Postdoctoral positions supported by external funding

SAIA (Slovak Academic Information Agency), National Scholarship Programme of the Slovak Republic: Ekaterina Nikitina (01.02.2012-30.09.2012)
Dr. German Gill, Universidad Nacional de Córdoba, Argentina (25.11.2014 – 12.12.2014)
Dr. Raquel Rubio, University of Philippines, (11.5.2015 - 15.5.2015)

2.8.2.3. SAS stipends and SASPRO stipends

Bábelová Andrea, Ph.D.
Functional consequences of renal cell activation due to iron oxide and gold nanoparticle uptake
0084/01/02, 1.8.2015 / 31.7.2018

Čipák L**uboš, Ph.D.**
Identification of substrates of essential protein kinases using shokat mutants
0032/01/02, 1.4.2015 / 31.3.2018

Jakubíková Jana, Ph.D.
Clonal dynamics of multiple myeloma
0064/01/02, 1.9.2015 / 31.8.2018

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

Michaela Fajtová, Ph.D. (01.01.2013-01.09.2013)
Marína Cihová, Ph.D. (05/2014-09/2015)

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

CRI SAS is an accredited organization for working with mutagens, carcinogens and performing experiments with genetically modified organisms (Class I and Class II). CRI SAS possesses certified animal facility (SK PC 14011) for breeding mice and rats. It is equipped with two semirigid isolators facilitating to perform projects on immunodeficient models (athymic and SCID mice).

The research infrastructure of the CRI SAS is at a disposal for other scientists who are interested in collaboration with our experienced users. The collaboration was mainly performed in the frame of common research projects and joint applications for the research grants, in order to cover the costs for the infrastructure usage.

CRI SAS possesses unique infrastructure that includes:

- Incucyte Zoom™ FLR – live-cell imaging system with two fluorescence detection modules with optional hypoxic conditions
- METAFER slide scanning platform for automated microscopic image analysis applications
- BD Canto II flow cytometer
- Image STREAM multiparameter cytometry with light microscope imaging single cell morphology
- FACS Aria – multicolor cell cytometer and fluorescence-activated cell sorter for cellsorting
- PALM MicroBeam Laser Capture Micro-dissection (LCMD) system with Zeiss fluorescent microscope

- PyroMark Q24 ID sequencing and quantification platform suited for epigenetics and mutation gene expression analysis
- The Enzyme-Linked ImmunoSpot (ELISPOT) system for monitoring cellular immune responses in humans
- NanoSight LM10 instrument for nanoparticle characterization
- Wave DHPLC System uses denaturing high performance liquid chromatography (DHPLC) for identification of the point mutations in analysed DNA fragment
- Cryotom Hyrax C50
- Microtom Hyrax M40
- Luminex platform for multiplex cytokine analysis
- NeonTM transfection system (nucleofector)

The Institute possesses fully equipped laboratories for aseptic work with tissue cultures (including biohazards, laminar safety cabinets (BSLII), CO2 incubators *etc.*), laboratories with all facilities required for work with bacterial and yeast cells and laboratories for molecular, genetic and biochemical research. Other equipment available at the Institute is ABI PRISM 310 Genetic Analyser for DNA sequencing, MIROClassic Complete 2-dimensional electrophoretic system for 2-dimensional electrophoretic separations, Real-Time PCR Cycler CFX96, Electroporation Pak BTX ECM399, CHEF-DR® III System for pulsed-field gel electrophoresis, microscope with CCD camera, CytoSpin cytocentrifuge, Fluorimeter PolarStar Optima and Luminometer LUMIstar.
Other standard equipment in the possession of the Institute are: many different kinds of centrifuges, spectrophotometers, pH meters, analytical balances, horizontal and vertical electrophoresis apparatuses for DNA and protein work, PCR cyclers, water baths, blotting equipment, electric power supplies, densitometers, transilluminators, thermoblocks, mixers, autoclaves, drying-ovens, sterilizators, laboratory deep freezers, and many other standard devices.

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

<u>Recommendations from the previous evaluation:</u> The Evaluation Panel appreciates the Institute's strong commitment to cancer research that has resulted in new ideas and scientific initiatives in the evaluated period. The Panel appreciates publication in highly ranked journals; however, the Panel feels that in some of them the Institute does not play a leading scientific role. Panel identified relatively low publication output as a weaknesses of the Institute. Specific recommendations were:
1/ To increase the number of peer reviewed papers per FTE/year while keeping the quality.
2/ Collaboration with clinics should result in clinically oriented publications.
3/ Recommendation: Increase in the number of peer reviewed papers per FTE/year should result in an increase of citations.
4/ Actively consider establishing bioinformatics programs/initiatives.
5/ Increase teaching appointments/activities with the Faculty of Medicine
6/ Seek regular contacts with clinical oncology community.
7/ Panel recommends the Institute to motivate young researchers to obtain DrSc. degree.

How results and suggestions from previous assessment was taken into account

The CRI SAS in the evaluated period 2012-2015 implemented the recommendations from the evaluation panel. In the list of publications from the Institute there were included the ones, where the Institute's researchers are in the leading position as a first or senior/corresponding author and the work was supported by the institutional grants. Other publications co-authored by the researchers from the CRI SAS in collaboration are listed in the supplementary information.

We have managed to increase the scientific output in the number of publications in 2015 in comparison to 2013-14; and overall we were able to keep the scientific production in the evaluated period similar as in the previous evaluation period. We would like to point out the increasing citation number of the publications with the Institute in the leading role, which reflects the significance of the

publications and their impact on the scientific community. Top cited publication with all authors from the Institute reached 133 citations in the evaluated period (Kucerova et al., Cancer Research 2007) and it was recognized as the third most cited research publication in Slovakia (Fiala & Ho, CURRENT SCIENCE, 110(1524):8, 2016,DOI: 10.18520/cs/v110/i8/1524-1531).

Several publications were prepared in collaboration with oncology clinics and their number increased significantly in the evaluated period. The collaboration is most intense with the Translation Research Unit of the National Cancer Institute and the Department for Research at the St. Elizabeth Cancer Institute. These collaborations were the basis for several joint project proposals and remain very active on both formal and informal personal level.

In order to initiate and conduct bioinformatics, prof. Igor Jurisica, PhD, Ontario Cancer Canter, IBM Life Sciences Discovery Center, Toronto, Canada, was invited to give a lecture and establish collaboration with his team within the ongoing research projects. As it was not possible to engage a full-time expert on bioinformatics at the Institute, we have undertaken the strategy of collaboration with researchers from the Department of Nuclear Physics and Biophysics, Faculty of Mathematics, Physics and Informatics, Comenius University, Bratislava, Slovakia. Their help with the data analysis resulted in scientific output already (Matuskova et al. J Gene Med., 2012). The group of I. Fridrichova has long-term collaboration with Dr. I. Wsolova, the Institute of Biophysics, Informatics and Biostatistics of the Slovak Medical University Bratislava. Her contribution was acknowledged in Fridrichova et al. (Transl. Res. 2015) and she is also a co-author of the publication by Smolkova et al. (Mutat Res. 2015). There is an ongoing collaboration with the group of prof. Hemminki, Division of Molecular Genetic Epidemiology, DKFZ Heidelberg, who executed statistical analysis of genotyping data as published already in Hemminki et al. (Genes Chromosomes Cancer 2015) and Vodicka et al. (Carcinogenesis 2015) co-authored by our colleague Dr. B. Smolkova. Also, a collaboration with Matej Stano, PhD., from the Institute of Molecular Biology SAS, who has a strong expertise and skills in the field of statics and bioinformatics, has recently been established to evaluate OMICS data produced during realization of APVV-0016-11 project.

We attempted to increase teaching appointments and activities with the Faculty of Medicine in Bratislava and Martin, based on their demands and invitations. Moreover, Dr. A. Babelova participates in providing seminars in Physiology for medical students of Medical Faculty of Goethe University, Frankfurt am Main, Germany, organized by the Cardiovascular Physiology Institute in the frame of the Center of Physiology - http://www.physiologie.uni-frankfurt.de/Engl/. (http://www.physiologie.uni-frankfurt.de/ZphysInhalt/Studierende/Sommer%202016/Seminar%20Teil%20I/Vorlesungs-Seminarplan%20Physiologie%20SS%2016.pdf)

As recommended from the previous evaluation, regular formal and informal contacts with clinical oncology community were intensified. CRI SAS annually participated in organizing Bratislava Oncology Days, with its own experimental session and lectures prepared by the Institute's researchers. Moreover, we also participated by several invited lectures on a regional meeting SEKCAMA dedicated to breast cancer treatment. The researchers from the CRI SAS prepared series of educational interactive workshops ONKOFORUM meeting in collaboration with pharmaceutical company in order to present recent scientific information and educate clinical oncologists in molecular oncology. Meetings were held in Bratislava on December 6-7, 2013, Košice on May 14, 2014 and Nitra on November 20, 2014. These meetings of the researchers and clinical oncologists enabled initiation of cooperation and increased interest and involvment of the clinicians to participate on research studies.

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

The management of the CRI SAS decided to perform organizational change starting on February 1st, 2014, which was approved by the scientific board of the Institute. Former Laboratories

were integrated into two departments: Department of Molecular Oncology (Laboratory of molecular oncology, Laboratory of tumor immunology, Laboratory of radiobiology) and Department of Genetics (Laboratory of molecular genetics, Laboratory of cancer genetics, Laboratory of mutagenesis and carcinogenesis). These two departments have integrated two main research directions at the Institute under the leadership of young researchers Lucia Kucerova, Ph.D., and Miroslav Chovanec, Ph.D., respectively, who became two vice-directors of the Institute. Subsequently, Lucia Kucerova, Ph.D., became director of the Institute beginning on April 1st, 2015 after the second 4-year period of the directorate by Jan Sedlak, D.Sc.

Long-lasting cumulating problems with the old buildings at Vlarska, Kramare, as described in the evaluation questionnaire 2007-2011, led to a strategic decision to build a new facility for the biomedical institutes of the Slovak Academy of Sciences in 2012 to integrate the personnel and infrastructure in one place for better cooperation of the teams with similar methodologies and enable closer contacts within the community along with the up-to-date research space. The project of Biomedical Park was successfully finished in 2015, and at the end of this period the Cancer Research Institute moved into the Pavilion of Medical Sciences in Bratislava – Patronka to the close vicinity of the Virology Institute SAS and other SAS institutes and facilities.

The Panel in the previous accreditation appreciated the appointment of young researchers as team leaders and identified them as candidates for the DrSc. degree. There was an increase in the minimum scientometric criteria to achieve the D.Sc. in addition to the obligatory condition for supervising PhD student who successfully finished doctoral study for the candidates, therefore there were no applicants within the evaluation period. However, there are several researchers – potential applicants, who will fulfill the necessary criteria very soon. There was a very important milestone in the CRI SAS personnel development, when 3 SASPRO applicants were successful and started to work at the Institute in 2015. These will build their research groups soon and collaborate with the researchers at the Institute to pursue their projects. We believe that they will be able to attract motivated students and help the postdocs in both experimental work and preparation of grant proposals in addition to their personnel development and growth.

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

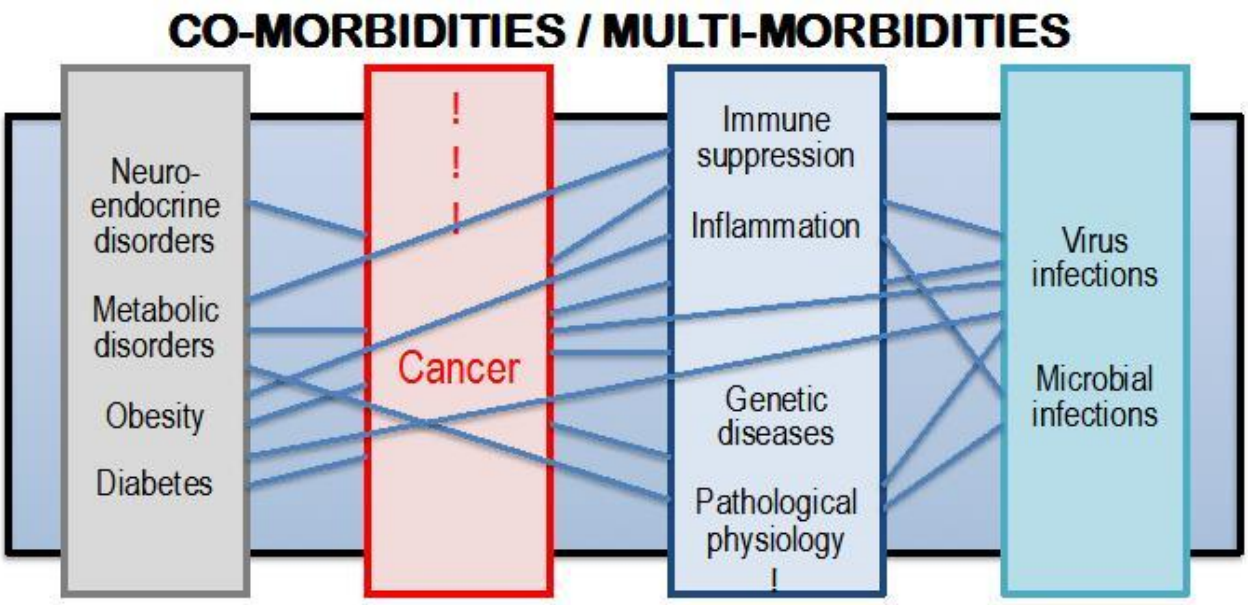
From January 1st, 2016, the Cancer Research Institute has become an integral part of the Biomedical Research Centre of the Slovak Academy of Sciences (BMC SAS), together with three other SAS institutes, namely the Institute of Virology, the Institute of Experimental Endocrinology and the former Centre 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 Cancer Research Institute is described in the context of the BMC SAS and the Part 3 of the Questionnaire is common for all four BMC SAS institutes.

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

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



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

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

VIRAL and MICROBIAL INFECTIONS

Institute of Virology

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

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

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

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

CANCER

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

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

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

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

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

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

STRESS, NEUROENDOCRINE DISORDERS, AND DEPRESSION

Institute of Experimental Endocrinology

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

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

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

endocrinologists and its scientists contributed to this area by a number of highly cited papers, some of which can be considered seminal for the development of this field.

METABOLIC DISORDERS, OBESITY AND DIABETES

Institute of Experimental Endocrinology and Institute of Clinical and Translational Research

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

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

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

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

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

GENETIC AND INFLAMMATORY DISEASES

Institute of Clinical and Translational Research and Institute of Experimental Endocrinology

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

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

oncologic (CRI) disorders, using state of the art genomic technologies. The BMC researchers also develop international activities through participation in EU networks aimed at characterization of monogenic disorders.

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

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

CO-MORBIDITIES / MULTI-MORBIDITIES

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

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

This brief overview shows that the research activities at BMC SAS, which are largely focused on chronic non-communicable diseases accounting for almost three quarters of deaths worldwide, correspond to the most recent state of the art in the biomedical field and react to global as well as national challenges of healthcare and society. At present, the BMC SAS stands at the crossroad that converges all experiences, skills and infrastructure, interconnects networks of existing collaborations, but also opens new directions for interdisciplinary approaches towards more complex knowledge on human diseases translatable to practice. As the most robust institution of this type in

Slovakia, the BMC SAS is now becoming increasingly attractive to clinical partners, which already expressed their interest for more close cooperation in areas that urgently need solutions in our country and which have far reaching implications for basic knowledge.

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

Basic information on BMC SAS
In the course of 2015, 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, known worldwide as non-communicable diseases (NCD), represent major socio-economic burden and health-care expenses also in Slovakia, and therefore, their control and management requires both basic research and translational approaches. Moreover, these pathologic situations, so far perceived as individual entities, often co-occur in the same organism and indeed, global biomedical research of the 21st century faces co-morbidities (or multi-morbidities) as one of the key challenges of the human health and quality of life improvement. It is becoming more apparent that viruses readily infect humans, which are obese or suffer from cardiovascular or metabolic problems, that virus infection can even contribute to obesity and vice versa, that obesity facilitates progression of cancer and development of metabolic and cardiovascular disorders etc. This complex view on co-occurring disease, on their cross-talk (e.g. how infections develop in obese organism, how obesity modifies response to anticancer therapy, how neuroendocrine imbalances affect cardiovascular system etc.) opens a new space for the closer collaborations inside the BMC SAS, using existing models, methodical approaches and knowledge. This inter-institutional cooperation will receive a maximum support of the Managing board of the BMC SAS.

Complementarity of infrastructure

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

will, however, require investments and intesive care for the sustainable development of this infrastructure as discussed below.

Concentration of excellent research teams and experts

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

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

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

Critical mass of projects and capacities

In conjunction with the concentration of experts and teams, the BMC SAS has received a large project portfolio, composed mainly of the relatively high number of projects funded by the very competitive national grant agency APVV (including the new grants awarded this year). In addition, the portfolio contains several international projects comprising the highly prestigious EU FP7 and H2020-funded projects, albeit their number is lower than in the past. The projects funded by the EU Structural funds in the first program period were completed last year and are currently not active.
Thus, the BMC is now at the starting point of the competition for new projects. The rich project history as well as excellent research capacities and topics relevant for H2020 strategy and national RIS3 strategic priorities represent good prerequisites for the new project proposals, which are currently in the process of elaboration and submission by the leading BMC scientists.

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

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

BMC SAS institute	Project proposals submitted to 7RP or H2020	2012	2013	2014	2015
Cancer Research Institute	Institute as coordinator	0	0	0	**1**
	Institute as participant	**1**	0	**1**	**3**

Institute of Experimental Endocrinology	Institute as coordinator	0	0	0	0
	Institute as participant	0	**1**	**2**	0
Institute of Clinical and Translational Research	Institute as coordinator	0	0	0	0
	Institute as participant	0	0	0	0
Institute of Virology	Institute as coordinator	0	0	**1**	**3**
	Institute as participant	**12**	0	**4**	**5**

Coordinated approach to challenges of sustainable development

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

Construction and management of the budget

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

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

Consolidation of personnel

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

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

Negative motivation is also problematic, because most of the salaries are at the very basic level. Moreover, the institutes have got permanent contracts with some researchers (enabled by past legislation), and this creates legal disadvantages for any contractual changes. The situation can be solved by the step-wise restructuring of the research groups, through the

staffing policy taking into account personal interaction and mutual benefit. However, this intervention is very case-sensitive due to big number of contracted running projects that require continuous research work and capacities to reach the goals.

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

Convergence and optimization of supporting units

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

Common interests

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

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

Conclusion

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

4. Other information relevant for the assessment

Cancer Research Institute of Biomedical Research Center SAS

CRI SAS represents established research institution in Slovakia with 70-year historical continuity performing basic and translational research. The CRI SAS represents a facility with several state-of-the-art platforms to enable pre-clinical studies. The CRI SAS cooperates with the clinical institutions in bedside-to-bench and reverse workflow. The orientation of the research on cancer survivors is recognized as an important task to follow, as there will be a substantially increasing proportion within the population with a need for specific care and tertiary cancer prevention measures. Our major aim is to contribute to development of targeted and tailored treatment for patients.

Our research strategy within the newly established Biomedical Research Center will be firmly connected to the established areas of interest, unique expertise and stable personalities of the Institute.

In particular, there are several unique personalities in the CRI BMC SAS who represent a guarantee of scientific progress and pursue perspective directions in their particular areas of interest.

Lucia Kucerova, Ph.D., (age 43, H-index 11, 38 articles in WOS, ≥ 963 citations), currently a scientific director of the CRI BMC SAS, became a leader of the research group with significant scientific output in the field of anticancer therapy by prodrug-activating mesenchymal stromal cells and the role of the mesenchymal stromal cells in intratumor heterogeneity.

Miroslav Chovanec, Ph.D. (age 47, H-index 14, 38 articles in WOS, ≥ 668 citations) is a leading scientist of the Department of Genetics and focuses on both mechanistic aspects of DNA damage and potential implications in clinical practice. His research interests cover both study of the repair of chemotherapy-induced DNA damage on yeast models and identification of biomarkers associated with treatment resistance in testicular germ cell tumors on patient material.

Lubos Cipak, Ph.D., (age 40, H-index 18, 52 articles in WOS, ≥ 768 citations) as a SASPRO guest scientist is expected to establish a scientific team focused on the role of essential protein kinases in regulation of meiotic chromosome segregation.

Jana Jakubikova, Ph.D., (age 40, H-index 17, 42 articles in WOS, ≥ 952 citations) as another SASPRO scientist and a coordinator of the ERA-NET consortium focuses on the research of clonal dynamics of multiple myeloma by unique progressive mass cytometry methodology. Her ERA-NET TRANSCAN-2 project “Multiple-myeloma intra-clonal heterogeneity: evolutions and implications of targeted therapy” is based on the collaboration with Greece, Israel and Poland.

Assoc. prof. Igor Beliaev, D.Sc. (age 55, H-index 16, 42 articles in WOS, ≥ 563 citations) is a leading scientist of the radiobiology research. His research will specifically monitor the DNA damage and preleukemic clones in hematopoietic stem cells in diagnostic, risk assessment and treatment of childhood leukemia.

Andrea Babelova, Ph.D. (age 40, H-index 16, 29 articles in WOS, ≥ 910 citations) as a SASPRO guest scientist is a member of the group which shifted their research interest towards the interactions of nanomaterials with human cells. Specifically her project is focused on functional consequences of renal cell activation due to iron oxide and gold nanoparticle uptake.

Alena Gabelova, Ph.D. (age 61, H-index 14, 62 articles in WOS, ≥ 619 citations) is a group leader who focused her research efforts towards the development a screening platform for nanosafety assessment with mechanistic functionality. She is a responsible person for the project H2020 entitled High level Integrated SEnsor for NanoToxicity Screening (HISENTS) coordinated by prof. Andrew Nelson, University of Leeds, UK. The CRI BMC SAS is one of the partners in this project.

We will be able to interconnect cancer research with the other branches of research within the BMC and this might represent unique strong platform to pursue strategies leading to decrease in the socio-economic burden of non-communicable (chronic) diseases in Slovakia.

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