Questionnaire

Summary of the main activities of a scientific Organisation of the Slovak Academy of Sciences

Period: January 1, 2007 - December 31, 2011

I. Formal information on the assessed Organisation:

1. Legal name and address

Ústav experimentálnej onkológie Slovenskej akadémie vied
(Cancer Research Institute of Slovak Academy of Sciences)
Vlárska 7
833 91 Bratislava

2. Executive body of the Organisation and its composition

Directoriat	name	age	years in the position
director	Ján Sedlák, DSc.	54	5
deputy director	Miroslav Piršel, PhD	60	5
scientific secretary	Alena Gábelová, PhD	57	5

3. Head of the Scientific Board

Katarína Luciaková, DSc.

Annexes: *publications*; *citations*, *presentations*, *top 10* cited publications

4. Basic information about the research personnel

i. Number of employees with a university degree (PhD students excluded) engaged in research and development and their full time equivalent work capacity (FTE) in 2007, 2008, 2009, 2010, 2011 and average number during the assessment period

Assessment period	Number of employees with a university degree	Full time equivalent work Capacity (FTE)	Average number during the assessment period
2007	74	58	55
2008	74	55	61.5
2009	75	57	61.5
2010	70	58	59.96
2011	65	64	46.05

ii. Organisation units/departments and their FTE employees with the university degree engaged in research and development

Research staff	2007		2008		2009		2010		2011		average	
	No.	FTE	No.	FTE	No.	FTE	No.	FTE	No.	FTE	No.	FTE
organisation in whole	74.00	54.85	74.00	58.55	73.00	58.01	67.00	50.73	61.00	41.54	69.8	52.7
Laboratory of Molecular Oncology	13.00	6.25	13.00	9.90	13.00	9.83	14.00	8.58	13.00	8.63	13.2	8.6
Laboratory of Molecular Genetics	12.00	11.75	13.00	11.50	14.00	12.75	14.00	12.75	16.00	11.00	13.8	12.0
Laboratory of Cancer Genetics	14.00	10.75	14.00	10.15	14.00	10.20	11.00	6.15	8.00	5.16	12.2	8.5
Laboratory of Tumor Immunology	14.00	9.60	14.00	11.30	14.00	11.15	13.00	10.50	11.00	8.03	13.2	10.1
Laboratory of Molecular Biology	7.00	5.00	7.00	5.00	6.00	5.00	6.00	5.75	5.00	3.36	6.2	4.8
Laboratory of Mutagenesis and Carcinogenesis	12.00	7.75	11.00	9.00	10.00	8.25	9.00	7.00	8.00	5.36	10.0	7.5
Epidemiology Group	2.00	0.75	2.00	1.70	2.00	0.83	0.00	0.00	0.00	0.00	1.2	0.7

5. Basic information on the funding

i. Total salary budget[1] of the Organisation allocated from the institutional resources of the Slovak Academy of Sciences (SAS) in 2007, 2008, 2009, 2010, 2011 and average amount for the assessment period

Salary budget	2007	2008	2009	2010	2011	average
total salary budget (milions of EUR)	0.776	0.798	0.846	0.831	0.798	0.810

URL of the Organisation's web site

http://www.exon.sav.sk

[1] Objem mzdových prostriedkov bez odvodov do poisťovní so započítaním sumy miezd pracovníkov THS, ktorú organizácii poskytne ETO Úradu SAV. Rozpočet v Sk prepočítajte na eurá podľa konverzného kurzu 1€ = 30,126. (Podobne aj v ďalších tabuľkách.)

II. General information on the research and development activity of the Organisation:

1. Mission Statement of the Organisation as presented in its Foundation Charter

1. The research and developmental activities of the Cancer Research Institute of Slovak Academy of Sciences (CRI SAS) are focused on investigation of the basic etiopathogenic factors and molecular mechanisms involved in the neoplastic transformation of normal cells to cancer ones. The goal of the scientific research is to characterize the biological, biochemical, immunological and genetic properties, and phenotypic markers of malignant cells from the point of cancer, normal and pathological physiology, molecular biology and cytology.

2. CRI SAS deals with descriptive and analytical epidemiology of the cancer incidence in the Slovak Republic in relation to demographic and regional risk factors.

3. CRI SAS contributes to solution of serious and for the medical practice important problems related to development and utilization of the diagnostic and therapeutic methods, bio-preparations and medication in the prevention and treatment, as well as new technologies for specification of some cancer types diagnosis.

4. CRI SAS provides consulting and services related to the main research activities of the organization.

5. CRI SAS carries out PhD study program in the frame of the general valid and legal rules.

6. CRI SAS publishes results from the research and developmental activities in the periodical and non-periodical journals. The periodical and non-periodical editions are guided by resolutions of the Presidium of Slovak Academy of Sciences.

2. Summary of R&D activity pursued by the Organisation during the assessed period, from both national and international aspects and its incorporation in the European Research Area (recommended 5 pages, max. 10 pages)

CRI SAS is one of the oldest research organisations in the Slovak Republic. Research at the Institute is pointed to the latest topics which have an impact on understanding the mechanism(s) of cancer development, prevention, diagnosis and eventually treatment of cancer. CRI SAS is the leading organisation in the field of i) immunophenotyping of plasma cells, ii) molecular-genetic diagnostics of cancer predisposition (colon cancer, breast and ovarian cancer, thyroid cancer), iii) molecular mechanisms of DNA repair pathways, iv) mesenchymal stem cells, and v) chemical carcinogenesis and genetic toxicology in Slovakia. CRI SAS had played the leading role in the utilisation of the flow cytometry technique in the diagnostics of blood malignancies. Another pioneering role of the CRI SAS was in the molecular-genetic diagnostics of cancer predispositions (breast

and ovarian cancer, FAP, HNPCC, MEN-2) which plays a pivotal role in the choice of the optimal treatment protocol. Several topical molecular-genetic methods have been established at CRI SAS and some of them have already been introduced into cancer clinics. Nowadays, CRI SAS offers expert consultancies in immunophenotyping and molecular-genetic diagnostics of cancer predisposition for many hospitals and regional medical organizations in Slovakia. CRI SAS has a long-standing collaboration with the two cancer hospitals; the National Cancer Institute (NCI) and the St. Elisabeth Cancer Institute (SECI) and they together constitute a Comprehensive Cancer Center (CCC) in the Slovak Republic. The close cooperation among these organizations contributes to the more effective transfer of the results and knowledge from basic research into clinical practice.

CRI SAS is a member of the prestigious Organisation of European Cancer Institutes (OECI) and collaborates with a large number of outstanding national, European and US laboratories. In the context of the 'Lisbon strategy' to create a better overall framework conditions for research in Europe, the scientists of CRI SAS had participated in several European Framework Projects (FP projects); unfortunately only a few of them were funded, although most of them exceeded the evaluation criteria. CRI SAS is a member of the DNA Repair Network and the Comet Assay Network. The scientists from 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 assessing the EU-funded project proposals. CRI SAS has organized several scientific conferences and workshops, both at national and international level, where many outstanding scientists took part. Relevance of the research activities is best manifested by publications of results in peer-reviewed journals (mean IF=2.6), many in highly ranking international journals. Presentation at numerous international conferences gives support for the significance of the research at CRI SAS. Moreover, numerous PhD and post-doctoral students have been awarded travel grants and scholarships to attend scientific meetings or to stay in outstanding laboratories abroad.

During the assessed evaluation period, the research activities at CRI SAS have been focused on both the basic and translational cancer research.

The **Laboratory of Molecular Oncology (LMO)** has focused its research interests on cancer cell biology and interactive signaling between cancer cells, stroma and mesenchymal stem cells. We have explored the use of human mesenchymal stromal cells as targeted vehicles for tumor therapy. We have carried out interaction studies of human mesenchymal stromal cells and cancer cells to extend our knowledge of the mesenchymal stromal cell – cancer cell interaction. Research interests have been directed towards the exploitation of novel findings in clinical applications for therapy of inherited and acquired diseases in general, and targeted therapy of cancer in particular.

Adipose tissue-derived mesenchymal stromal cells have achieved considerable attention as delivery vehicles for bystander effect and cancer therapy. In our work, we have reported a capability of human adipose-tissue derived mesenchymal stem cells (AT-MSCs) to serve as delivery vehicles for yeast fusion cytosine deaminase (CDy)/5-fluorocytosine (5FC) in a proof-of principle study. Subsequently, we were able to confirm therapeutic efficiency in human colon adenocarcinoma, melanoma, prostate adenocarcinoma and medullary thyroid carcinoma xenograft models. However, in order to achieve higher tumor growth inhibition we have observed necessity to treat tumors by multiple CDy-AT-MSC doses. Moreover, we have expressed thymidine kinase HSV-TK in AT-MSCs to evaluate efficiency of TK-AT-MSCs/GCV against glioblastoma cell lines. Our data confirmed the requirement for functional gap junctional communication in order to achieve substantial bystander cytotoxic effect *in vitro*. Therapeutic efficiency was limited in an *in vivo* setting and did not achieve significant inhibition. *[Cancer Research 67, 6304-13, 2007; J Gene Medicine 10, 1071-82, 2008, Molecular Therapy 18, 223-31, 2010; Cancer Letters 290, 58-67, 2010; Cancer Letters 311, 101-12, 2011].*

In a parallel studies, we have focused on the role of non-malignant stromal cell in the tumor development. MSCs tropic properties for tumors may lead to polar opposite outcomes of tumor suppression or tumor enhancement. This outcome is a result of dynamic cross-talk between MSCs and tumor cells. The outcome of the MSCs and tumor interaction is most probably strongly dependent on the cellular context of interaction with direct impact on the extent of tumor inhibition. Based on these findings, we propose to modify the therapeutic strategy depending on the MSC-tumor cell interaction. Valuable scientific results were achieved in collaboration with the University and hospital research facilities and published during the evaluated time period. *[Molecular Cancer 9, 129, 2010; Neoplasma 58, 361-70, 2011; Stem Cell Research 8, 247-58, 2012]*

Research interest of the **Laboratory of Molecular Genetics (LMG)** has been focused on the understanding of molecular details of certain DNA repair pathways. During the assessed period, the LMG has studied the molecular mechanisms of DNA damage recognition during nucleotide excision repair (NER), a highly conserved pathway needed for the repair of ultraviolet light (UV)-induced DNA damage. *Pyrococcus abyssi* homologues of the human NER proteins, XPB, XPG and XPF, have been purified. In addition, PaXPD homologues carrying the mutations from XP-D patients have also been prepared. The LMG has currently been studying the helicase activity of the mutant XPD proteins, alone or in combination with XPB, the interactions among participating proteins, especially between XPD and XPG, and the effect of XPD mutations on incision of defined DNA substrates. The LMG has also been testing a possible involvement of the hamster ERCC3 protein (XPB in humans) and/or NER and/or TFIIH holocomplex in DNA damage response, checkpoint signaling and apoptosis. A set of hamster *ercc3* mutant cell lines displaying various degrees of UV sensitivity has been in use. The NER capacity, RNA synthesis recovery, apoptosis, cell cycle progression, replication-mediated DNA double-strand break (DSB) formation and chromosomal aberrations, have all been investigated. The data suggests that the preserved stability of the TFIIH complex in the most UV resistant *ercc3* mutant allows its participation in the cell cycle control and apoptosis [*Mutagenesis, 25, 179-185, 2010*].
Using *Saccharomyces cerevisiae*, the LMG has discovered a novel mechanism, dependent on Nej1 (a regulator of non-homologous end joining - NHEJ)-Srs2 (a helicase with role in homologous recombination - HR) interaction, which mediates cross-talk between these two DSB repair pathways. Both Srs2 and Nej1 are required for repair of DSB by single-strand annealing (SSA), a sub-pathway of HR. As the absence of Rad51 (the key HR factor) suppressed the SSA-defect in *srs2/nej1* cells, we suggest that Nej1 recruits Srs2 to DSB to promote SSA-like repair by dismantling inappropriately formed Rad51 filaments [*Proc. Natl. Acad. Sci. U.S.A, 106, 12037-12042, 2009*]. In yeast, interstrand cross-link (ICL) repair is dependent on the co-ordinated action of NER, HR and translesion DNA synthesis. Also, it utilizes additional factors such Pso2, which is a nuclease involved in repairing DSB that arise as result of replication fork collapse when an ICL is encountered. We have revealed the existence of a novel complex consisting of Msh2, Msh6, Mgm101, Mph1, Slx4 and Chl1 that has an overlapping function with Pso2-dependent arm of ICL repair during S phase [*PLoS Genet., 2011, submitted*]. The LMG has also worked on delineating the mechanisms of selenium toxicity in yeast with emphasis on the role of DNA damage repair. We have found that sodium selenite (SeL), in contrast to selenomethionine and Se-methylselenocysteine, manifests significant toxic and mutagenic effects in yeast. We suggest that these effects are associated with the ability of this compound to induce DSB, and hence that SeL produces oxidative damage to DNA accounting for the observed DSB and cell death [*Mutat. Res., 638, 1-10, 2008*]. Subsequently, we have uncovered factors that were responsible for repairing SeL-induced DSB and have reported that Rad52 is indispensable for this process, suggesting a fundamental role of HR in the repair of SeL-induced DSB [*Mutat. Res., 652, 198-203, 2008*]. A contribution of base excision repair (BER) and NHEJ towards genotoxic effects of SeL has also been examined. We show that cells impaired in BER are sensitized

towards the toxic effects of SeL. Finally, we have reported that NHEJ is not responsible for induction of short deletions observed after SeL exposure in our previous study [*Mutagenesis, 25,155-162, 2010*]. Also, we have used the combination of two genome-wide approaches, the yeast haploid deletion mutant library screen and transcriptome profile analysis by microarray, to delineate the mechanism(s) of Se toxicity in yeast with emphasis on the role of DNA damage response and repair pathways [*Chem. Res. Toxicol., 2011, submitted*]. Finaly, we have exploited *S. cerevisiae* as host for the expression of *Schizosacchamyces pombe atl1* gene to study the effects of Atl1 protein on the repair of alkylation damage to DNA in various DNA repair defective backgrounds (*mgt1, rad4, mag1, rad4 mag1*). The positive/negative effects of the Atl1 protein on the toxicity and mutagenicity of a variety of alkylating agent have been assessed by the survival experiments.
The development and validation of sensitive biomarkers to predict how breast cancer patients would response to radiotherapy that could lead to personalization and optimization of their treatment has also been in focus of the LMG in the assessed period. We have revealed that some foci produced by phosphorylated histone 2A family member X and p53 binding protein 1 (53BP1) that co-localize with radiation-induced DSB remain in cells a long time after irradiation and indicate a possible correlation between cellular radiosensitivity and residual foci [*Int. J. Radiat. Biol, 83, 319-329, 2007*]. Moreover, we have evaluated residual foci in human cells *in vitro* and in blood of breast cancer patients undergoing radiotherapy and have suggested that the residual foci may be useful for biological dosimetry and estimation of individual radiosensitivity in radiotherapy of tumors [*Mutat.Res., 704,132-141, 2010*]. We have also studied whether microwaves (MW) from mobile phones induce DSB or affect DSB repair in stem cells. We found that MW from mobile phones inhibit formation of 53BP1 foci in human lymphocytes, primary fibroblasts and mesenchymal stem cells, where the strongest effects of MW were observed. Our findings that stem cells are most sensitive to MW exposure may be important for cancer risk assessment [*Bioelectromagnetics, 30, 129-141, 2009; Environ. Health Perspect., 118, 394-399, 2009*].

Human cancer represents a heterogeneous group of diseases that are driven by numerous genetic and epigenetic events. In previous years, the **Laboratory of Cancer Genetics (LCG)** has introduced a set of determining molecular genetic methods for identification of germline-mutation carriers in patients suffered from hereditary forms of polyposis and non-polyposis colorectal cancer (FAP, Lynch syndrome - HNPCC), and breast and ovarian cancer and the results of analyses were used in patient management. In relation to our previous experiences, we have continued in research of molecular alterations in colorectal cancer and leukemia patients. The epigenetic gene silencing, namely DNA methylation in *MLH1* mismatch repair gene, was investigated in Lynch syndrome (LS) patients. Our results indicate that *MLH1* methylation could serve as an important discriminator between sporadic and hereditary unstable colorectal tumors with dense and weak promoter methylation profiles, respectively [*Genes, Chromosomes & Cancer, 47, 906-914, 2008*]. From genetic events we reported the first evidence of partial gene conversion in *MLH1* and *MSH2* genes that can cause the second allele inactivation and thereby DNA mismatch repair deficiency in colorectal tumors of LS patients (*BMC Cancer, 9, 1-15, 2009*). For evaluation of correlation between the presences of single nucleotide polymorphisms (SNP) in *MDR1* gene and drug response in acute myeloid leukemia patients we suggested three SNPs that are frequently occurred in Slovak population (*Neoplasma, 56, 101-107, 2009*). In other projects, we have focused on the role of the *APC* gene in colorectal carcinogenesis. FAP patients were tested for *APC* germline mutations and several SNPs. We found high incidence of polymorphism at codon 1822 in the *APC* gene that could be a specific feature of Slovak patients [*Neoplasma, 56,486-489, 2009; Neuroendocrinol Lett, 25-28, 2009*]. Moreover, we have developed the mouse model for APC deficiency complementation using bacteria expressing an active human APC protein. Next topic was initiated by supposing that

intracellular bacteria can play an important role in many diseases including cancer and AIDS. In HIV^+ patients from Kenya and Cambodia HIV-like sequences were detected in both intestinal bacteria and samples from throat swabs [*Neuroendocrinol Lett, 28,591-595, 2007; Med Sci Monit, 17, 154-158, 2011*]. In cell lines and normal human lymphocytes we observed the internalization of intestinal bacteria isolated from HIV/AIDS patients ten times more frequently in comparing with those from patients with colorectal problems. Our findings indicate some role of bacteria in AIDS development. In the study of probiotic bacteria impact in cancer therapy, we observed its preventing effects from febrile neutropenia and other negative side effects in paediatric cancer patients after the chemotherapy treatment. Furthermore, we investigated the modulating activities of several bioactive compounds in cancer chemoprevention and chemotherapy. We observed several differences in cytotoxic and therapeutic activities of cytosine arabinoside new analogs that could be the cause of problems in leukaemia and lymphoma therapy. Overall, the research interest has been focused on topics associated with more detailed molecular characterization of tumours that will lead to more effective management of cancer, including the use of novel molecular markers for early diagnosis or prognosis, and also new treatment approaches.

The research activities executed in the **Laboratory of Tumor Immunology (LTI)** has been focused on the molecular mechanisms in human cancer cells during cancer development, treatment, or growth inhibition. The use of molecular genetic, biochemical and immunological methods, together with the methods of flow cytometry, allowed us to create a complex picture of diverse human cancer cell populations and evaluate the importance of molecular processes associated with molecular targets for cancer therapeutics *in vitro* and *in vivo*. The research activity of the LMI has been focused on several topics.

1. a) the relevance of the activation of MAPK signaling pathways during the release the synchronized leukaemic cells from the block at G(1)/S boundary by synthetic isothiocyanate (ITC), E-4IB, and followed by the induction cell cycle arrest and apoptosis; b) a synthetic ITC derivate indol-3-ethyl isothiocyanate (homoITC) as an effective modulator of cellular proliferation and inducer of apoptosis with the potential use as an anticancer drug or a sensitizer to chemotherapeutic agent cisplatin (CDDP) in human ovarian carcinoma cells and their CDDP-resistant variants; c) markers related to CDDP resistance associated with specific signaling/apoptotic pathways and the potential of transcriptional NF-κB/proteasomal regulation of CDDP-resistance molecules, as molecular targets for the single- or combined *in vitro* and *in vivo* chemotherapy**).** d) new therapeutical approaches and prognostic markers in human breast and ovarian cancer cells associated with the signaling pathways that affect the course of the disease and development of antitumour immunity and aggressive phenotype modulated by natural compound isothiocyanate (ITC) sulphorafan [*Cell Prolif 2007, 40(3), 316-326; Neoplasma 2009, 56(3), 208-214;; Neoplasma 2009, 56(6), 548-556; Neoplasma 2010, 57(5), 473-481*].

2. a new sensitive, quantitative method based on flow cytometry to measure NK-mediated cytotoxicity *in vitro*, the effects of a food supplement BioBran (MGN-3 arabinoxylane) in human innate immune cells upon *in vitro* differentiation and maturation of key antigen-presenting dendritic cells (DC), and its effects on innate immune system of multiple myeloma (MM) patients in a randomized, double-blind and placebo controlled study. Further, high capability to bind bacterial ghosts (BG) was observed in almost all of the analyzed cell cancer lines, where cells were able to take up BG independently of the used bacterial species [*Immunobiology 2008,213(8), 629-640; Cancer Lett, 2008, 262(1), 54-63; Neoplasma 2009, 56(2), 89-95*]**.**

3. realgar (As4S4) cytotoxicity in different nanoparticle fractions and selection sensitive cell lines for the synergy treatments between realgar and ITCs, and mechanisms of apoptosis in xenotransplant mouse models [*Materials Letters 2009, 63, 1542–1544*]**.**

4. a) non- classical HLA class I (ectopic HLA-G) distribution and regulation by epigenetic effects, i.e. DNA demethylation and histone acetylation in normal tissues and at pathological conditions, such as in virus infected or tumor cells; b) the effect of stress (heat shock and hypoxia) on HLA-G transcription resulting in the fact that demethylating treatments led to HLA-G transcription in several leukemia cell lines and also to enhanced HLA-G transcription and concomitantly HLA-G protein synthesis in some malignant hematopoetic cells isolated from patients with acute myeloid leukemia (AML) and chronic lymphocytic leukemia (B-CLL); c/ sHLA-Gs (sHLA-G1 and HLA-G5) in different blood samples of healthy donors, where the levels of sHLA-Gs in blood plasma prepared with EDTA were significantly higher than those observed in plasma with heparin or in serum and the average levels of sHLA-G in females exceeded those of males [*Leuk Res 2009, 33(4), 518-524; Neoplasma 2009, 56(6), 508-513; Neoplasma 2011, 58(4), 337-342*]**.**
5. a) membrane/intracytoplasmic markers of T-, B-lymphoid lineage and myeloid leukemic cell patients and populations of leukemia blasts and regenerating cells, hematogones (multiparameter flow cytometry); b) membrane and intracellular markers of acute leukemia and lymphoma cells of T-phenotype, i.e. prognostic factors for the follow-up of T-ALL/T-NHL in remission. The results showed that patients with the more favorable prognosis could be distinguished from those allocated to pro-T stage with very immature phenotypes and an unfavorable clinical course [*Leuk Lymphoma 2008, 49, 1935-1944; Neoplasma 2009; 56(6), 508-513*]**.**
6.mapping (by transmission electron microscopy) the location and characterization the nucleoids and specification their binding to the inner and the outer mitochondrial membranes. The results showed that mitochondrial genomes together with many specific proteins are organized in mitochondrial nucleoids [*Gen Physiol Biophys 2010, 29(2), 160-174*]*.*

Research at the **Laboratory of Molecular Biology** had been focused towards elucidation of the molecular mechanism(s) leading to: 1) growth arrest and 2) apoptosis. As a part of a larger European 6th Framework project a part of the Laboratory was involved in studies of lipid and cholesterol metabolism in development of atherosclerosis and the role of the transcription factor HNF-4 in the regulation of cholesterol metabolism.
During the development of an organism, its cells need to proliferate, differentiate, rest and die. Most cells in an organism remain in a reversible resting state, the quiescent (G0) state. Depending on the external signals, these quiescent cells may re-enter the cell cycle, may differentiate, may become senescent and eventually die. Higher eukaryotes have evolved multiple check point mechanisms to monitor and respond to the signaling. Errors in any of these control mechanisms are detrimental to the integrity of the genome and may promote cancer development. Our research is focused on the mechanism(s), as well as the signaling pathways governing the regulation of transcription. We recently described a unique role for nuclear factor-1 (NF1) as an active repressor of gene expression in growth-arrested human diploid fibroblasts using the human adenine nucleotide translocator-2 gene (*ANT2*) as a model [*Biochem. J. 412, 123-130, 2008; Gen. Physiol. Biophys. 28, 331-339, 2009*]. We studied the molecular mechanism by which NF1 inhibited the expression of ANT2 and how this function was integrated into existing signaling pathways [*Biochem. Biophys. Res. Commun.411, 648-653, 2011*].
Apoptosis plays an important role in many physiological processes and its misregulation is linked to serious diseases. Since it is known that inhibition of cell death is a common event in tumor development, we wished to understand factors regulating the programmed cell death. Moreover, successful chemo- and radiotherapy of cancer depends, to some extent, on the ability of tumor cells to undergo apoptosis. Our research was focused on studying the molecular mechanisms which control the induction of apoptosis, with emphasis on the key players of the mitochondrial pathway of apoptosis, the family of Bcl-2 proteins. Although yeasts do not have homologues of these proteins, expression of mammalian proteins of the apoptotic pathway induces cell death. Thus, they could be

used as a simple model to study whether a knock-out or over-expression of selected cellular proteins is able to modify the apoptotic effect of Bax.
Inhibitors of histone deacetylases are already in clinical trials as potential anticancer drugs. Our data suggest that histone deacetylation and histone deacetylases play also a role in lipid metabolism. Aberrant lipid and cholesterol metabolism represents a basis for the widely spread human disease: atherosclerosis. Cholesterol and lipid homeostasis is achieved through the action of a complex regulatory network that controls the expression of genes involved in these metabolic pathways. Our recent studies suggest that high in the hierarchy of the regulatory network is the nuclear receptor HNF-4, whose activity on genes of cholesterol metabolism is selectively affected by HDAC7 recruitment. Given this premise, the general aim is to bridge the new basic science concepts to clinical applications by analysing the transcriptome and the regulome controlling cholesterol and lipid homeostasis and by pharmacologically targeting the HNF-4/HDAC7 regulatory axis. These results were published in excellent, high-impacted journals [*Mol. Endocrinol. 21, 2085-2098, 2007; Nature 452, 45-50, 2008; Bioorg. Med. Chem. 17, 7021-7030, 2009*].

The research activities of the **Laboratory of Mutagenesis and Carcinogenesis (LMC)** have been focused on various current research problems related to i) molecular and cellular mechanisms of chemical carcinogenesis, genetic toxicology and nanotoxicology, ii) chemopreventive and chemoprotective potential of natural substances, iii) intrinsic radiation toxicity and iv) computer-assisted combinatorial chemistry. A great attention has been devoted to molecular and cellular mechanisms of chemical carcinogenesis with emphasis on the tissue specificity of chemical compounds. Structure-activity relationship, DNA damage profile determination and the role of drug-metabolizing enzymes in biotransformation of chemical compounds were dominant topics investigated in this field. Heterocyclic aromatic hydrocarbons represent a relatively minor fraction of the crude organic mixtures of environmental pollutants. These compounds may, however, pose a serious carcinogenic risk to humans due to their intrinsic biological activity. *7H*-Dibenzo[c,g]carbazole (DBC), a ubiquitous environmental carcinogen, is a potent multi-species and multi-site carcinogen with both local and systemic effects. In contrast, its methyl derivatives, *5,9*-dimethylDBC (DiMeDBC) and *N*-methylDBC (N-MeDBC), showed specific tropism for the liver and skin, respectively. Despite a close similarity in the chemical structures, different molecular mechanisms underlie genotoxic and non-genotoxic effects of the liver carcinogens DBC and DiMeDBC in the liver cell line, WB-F344 [*Mutat Res 665, 51-60, 2009*]. In contrast to DBC, the reactive oxygen species (ROS) generated in DiMeDBC-exposed liver cells might underlie the biological activity of this strict hepatocarcinogen. Our data clearly demonstrated that the genotoxicity of DBC derivatives in human liver cells, HepG2 has been closely related to cytochrome P450 (CYP) 1A1/2 expression [*Environ. Mol. Mutagen. 52, 636-645, 2011*]. Previous *in vitro* studies have convincingly demonstrated that P4501A family of enzymes is involved in DBC biotransformation. Recently, we have shown that hCYP3A4 might also play an important role in hepatocarcinogenic but not sarcomagenic DBC derivatives [*Toxicol Appl. Pharmacol. 255, 307-315, 2011*].
The research staff of LMK has contributed to the risk assessment of complex organic mixture (EOM) associated with the respirable airborne particles (PM10). The ambient air pollution is a matter of great interest all over the world because millions of people are chronically exposed to low doses of noxious chemicals. Our *in vitro* study clearly demonstrated that EOM were genotoxic [*Mutat, Res., 620, 103-113, 2007*]; however, they did not induce any significant levels of oxidative damage to the DNA. Therefore, the free radical generating activity of airborne particles might not contribute to the adverse effects of PM10 [*Mutat. Res., 620, 135-144, 2007*]. However, organic compounds can undergo various interactions (additive or synergistic) with other components in the mixture and in this way they might enhance/multiply the adverse health effect of air pollution on humans.
The rapidly emerging fields of nanoscience and nanotechnology triggered discussions about the potential negative adverse effects of engineered nanoparticles (NPs, particles

typically <100 nm in size) on human health and ecosystem. In medicine, NPs are the subject of fast-moving developmental efforts aimed at the improvement of diagnosis and treatment of cancer. A great effort has been focused on magnetite nanoparticles (MNPs) as magnetic resonance imaging contrast agents, heating mediators in hyperthermia cancer therapy or as nanovectors for targeted delivery of drugs/genes into malignant tissues. MNPs are physiologically well tolerated; moreover, the superparamagnetic properties of MNPs are eligible for delivery of the drug-loaded MNPs in the target site *via* an external magnetic field. Consistent with worldwide trends, we have studied the biological activity of MNPs with different surface modifications. MNPs were synthesized and characterized in-depth. We have found differences in the internalized quantity of MNPs, cell viability and genotoxicity between human lung tumor (A549) and diploid (HEL 12469) cells. The weak MNPs uptake into A549 cells might be of biomedical relevance in cases where MNPs should be used as nanocarriers for targeted drug delivery into tumor tissue derived from alveolar epithelial cells [*Neoplasma 2012 in press and unpublished results*].

Though numerous studies have suggested that natural compounds are very beneficial to human health and may decrease the risk of many types of cancer and so-called civilization diseases, some contradictory results were obtained in epidemiological and molecular-epidemiological studies. This fact stimulated a great need for more extensive and deeper knowledge about the role of natural compounds on different features of living systems. In the frame of the projects completed in the years 2007-2011, we have 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 dangerous cellular effects in different types of mammalian cells. We proved significant DNA-protective activity in the case of fungal cell wall polysaccharide carboxymethyl chitin-glucan, lignin biopolymer and several components of essential oils (carvacrol, thymol, borneol and rosemary oil). For the measurement of different kind of DNA damage and their levels, we used the alkaline single cell gel electrophoresis as well as several modifications of this method. Computerized image analysis system was used for determination of DNA in the tail, which is linearly related to the frequency of single strand DNA breaks. Results published in peer-reviewed journals underline the relevance of such research activity [*Nutrition and Cancer 57, 2007, 209-215; Food and Chemical Toxicology 47, 2009, 1318-1323; Mutation Research 677, 2009, 46-52; Food Chemistry 123, 2010, 151-156; Toxicology in vitro 24, 2010, 1986-1992*].

The integrity of the genome is crucial for tumor suppression and for the propagation of genetic information to subsequent generations. Genomic instability in the form of chromosome rearrangements (chromosomal instability) is usually associated with pathological disorders and is a characteristic of almost all human cancers. Genomic instability induced by ionizing radiation might underlie the inter-individual variation in susceptibility of the cancer patients to radiotherapy. There is considerable evidence that radiation-induced genomic instability transmitted from an irradiated clonogenic cells may result in an `activated cell´ capable of inducing a bystander-mediated transmissible genomic instability or a damage response in an unirradiated clonogenic cell or in a cell that has descended from an unirradiated clonogenic cell. These effects are collectively known as radiation-induced genomic instability (RIGI). Tumors with higher RIGI levels are prone to develop the radioresistant subpopulations of cells. Another important question in radiation biology is the `adaptive response´ of cells to radiation. Cells preconditioned with low doses of ionizing radiation become more resistant to later challenges of radiation. Although the mechanism(s) remains unclear, it has been suggested that activation some of the DNA repair pathways by low doses of ionizing radiation might underlie the increased cellular radioresistance. An important goal of current research in radiation oncology is the development of an assay or a combination of assays to predict the response of individual human tumors and normal tissues to radiation. The wide

heterogeneity of cancer patient to radiotherapy is the main obstacle of effective tumor radiotherapy.

We have performed a cytogenetic monitoring (chromosomal aberrations and sister chromatid exchanges) in lymphocytes obtained from healthy donors and cervical cancer patients irradiated with different doses of X-rays or γ-radiation. The aim of this study was to investigate i) differences in the genomic instability, ii) adaptive response of cells after irradiation iii) changes in gene expression pattern by the CESH method (Comparative Expressed Sequence Hybridization), and iv) RIGI induction in both the non-cancer and cancer cells. In general, we have found higher levels of chromosomal aberrations in cancer patient cells compared with healthy donors, suggesting higher predisposed vulnerability of tumor cells. In addition, we have detected inter-individual differences in chromosomal instability in the patient cohort. Based on our results, cytogenetic analysis can be used for biomonitoring of cancer patient´ susceptibility to ionizing radiation.

Combinatorial chemistry has been developed to a stage where synthetic schemes are available for generation of a large variety of organic molecules. Computational methods are valuable in the design of virtual libraries of molecular models. Selection strategies based on computed physicochemical properties of the models. Such target of compounds is introduced to reduce the time and costs of library synthesis and screening.

We have participated in several computer-assisted drug discovery projects, which involved design of antiviral, antibacterial and anti-parasitic compounds. We have used quantitative structure-activity relationships and molecular modelling to design cationic antimicrobial peptides and studied proteins that bind components of the bacterial membrane of G^- bacteria. However, the main focus of the research was in the structure-based and combinatorial design and virtual screening of antiviral compounds. We have designed a set of peptidomimetic compounds with a transition-state-isostere –PheΨPro– core, which bind to and inhibit the aspartic protease of HIV-1 virus in the low nanomolar concentration range and are endowed with favorable ADME-related properties. In another series of papers prepared in collaboration with the Chulalongkorn University, Bangkok, Thailand, we have carried out combinatorial design and optimization of compounds (analogs of oseltamivir) which inhibit the neuraminidase of the avian influenza virus H5N1.

Based on a study of a training set of carbocyclic N1 inhibitors, we have developed a QSAR model that was used to select virtual hits with predicted inhibitory activities in the sub-nanomolar concentration range. In a parallel study, we have designed a virtual library of anti-influenza agents, containing a novel pyrrolidine core, which effectively inhibits both wild type and common oseltamivir-resistant mutant forms of the neuraminidase N1 in the picomolar range. Another research project on antiviral compound design was devoted to Dengue virus. We have used computer-assisted combinatorial techniques to design, focus and *in silico* screen a virtual library of peptidomimetic analogs targeted around the template inhibitor Bz-Nle-Lys-Arg-Arg-H carrying and aldehyde electophilic aldehyde warhead that is known to bind to NS2B-NS3 serine protease of the virus and blocks the viral replication. Antiparasitic (antimalarial) compounds which inhibit the enoyl-acyl carrier protein reductase, a key enzyme of the FAS-II pathway of lipid synthesis of *Plasmodium falciparum*, were designed starting from substituted analogs of triclosan. Results published in peer-reviewed journals underline the relevance of such research activity [*J Mol Graphics Modell 27, 376-87, 2008; Eur J Med Chem 44, 3009-3019, 2009; Antivir Res 82, 51-58, 2009; J. Comp-Aided Mol Des 24, 195-212, 2010*].

The research activities of the **Epidemiology Group (EG)** were focused on data collection and analysis in cooperation with National Centre of Health Information, participating in several international epidemiological projects of EU and in National Cancer Registry, till Dec 2009. The results were published in monographs and CC journals [*Nádorové ochorenia spôsobené užívaním tabaku. SAP Bratislava, 2007, ISBN 978-80-8095-0; Epidemiológia onkologických ochorení na Slovensku. Med-In Alfa, 2007, ISBN 978-80-969659, Neoplasma 55, 10-15, 2008; Eur J Cancer 46, 1528-1536, 2010*]

3. Concept of R&D activity of the Organisation for the next four years (recommended 3 pages, max. 5 pages)

i. Present state of knowledge and status of ongoing research related to the subject of the Concept, from both international and national perspective

CRI SAS represents a unique research institution in Slovakia which covers a wide research area of basic and translational cancer research. As an integral component of the Comprehensive Cancer Center, the CRI SAS represents a facility with several state-of-the-art platforms to enable multiple pre-clinical studies. Both on national and international levels, the researchers of the CRI SAS perform outstanding basic research in their particular areas of scientific interest. Moreover, the CRI SAS cooperates with the clinical institutions in order to focus on clinically relevant problems and analysis to allow both bench-to-bedside and reverse workflow. The orientation of research to the topic of cancer survivals is recognized as an important task to follow. Our major aim is to contribute to worldwide cancer research by pursuing approaches which enable the cancer treatment to be targeted and tailored to a specific patient's disease. Recently, our cooperation and research efforts have brought many original results which have been published in international journals with high impact. High number of citations reflects the relevance of the finding on the European and worldwide scale.

Overwiev of research performed at the Cancer Research Institute:

Laboratory of Molecular Oncology: Research of the Laboratory of Molecular Oncology is focused on cancer biology and interactive signaling among cancer cells, stroma and mesenchymal stem cells. Circumventing chemoresistance in tumor cells and achievement of the metastatic spread control still remain major hurdles in the treatment of malignant disease. Human multipotent mesenchymal stromal cells (MSCs) were proven to be efficient delivery vehicles for several enzyme/prodrug combinations to mediate bystander cytotoxicity toward various tumor types. We intend to apply evidence-based strategies to augment antitumor effect mediated by genetically modified MSCs in order to achieve eradication of chemoresistant cells which often share the properties of cancer stem cells.

Laboratory of Molecular Genetics: Research of the Laboratory of Molecular Genetics is aimed at the understanding of molecular details of some of the DNA repair pathways. DNA repair mechanisms are crucial factors of genome integrity and stability maintenance and they play an important role in pathogenesis and progression of various types of malignancies and other human disorders. In ongoing projects, we are studying molecular details of certain DNA repair pathways both in prokaryotes and eukaryotes. We shall continue our toxicology project aimed at uncovering the genetic factors responsible for selenium toxicity. Moreover, we shall also focus on personalization and optimization of cancer treatment as well as implementation of radiobiological research of intensity-modulated proton therapy into clinical oncology practice.

Laboratory of Mutagenesis and Carcinogenesis: In spite of advances in modern medicine which possess quantum of synthetic medicaments, a great importance is ascribed to 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 rapid expansion in the field of nanotechnology promises to have significant benefits to society, yet there is an urgent need for research determining key structural aspects affecting the interaction of nanoparticles (NPs) with biological targets, as well as the consequent health effects. In spite of enormous effort in nanotoxicological research in the last decade, a suitable *in vitro* screening for adverse effects of NPs has not been established. In line with

worldwide trends, Laboratory of Mutagenesis and Carcinogenesis will continue in research activities dealing with the understanding the nature of measured biological responses induced by nanoparticles at different levels of biological organization (from molecules to cells and animals) from which the potential risks to human health will be determined. A new project in the Laboratory is represented by studies of the molecular mechanism(s) of gene transcription under the conditions of cellular stress.

Laboratory of Cancer Genetics: Research interests of the Laboratory of Cancer Genetics are focused on molecular characterization of tumors which may lead to a more effective management of cancer including a use of novel molecular markers for early detection and prognosis. Determination of new strategies for cancer prevention and improvement of chemotherapy side effects in cancer patients using probiotics and prebiotics may help to design novel therapeutic approaches.

Laboratory of Tumor Immunology: The tumor immunology program is focused on studies of molecular mechanisms in human cancer cells during cancer development and treatment. The use of genetic and immunological methods, together with flow cytometry and qRT-PCR allows us to build a complex picture of diverse human caner cell populations and evaluate the importance of these molecular processes, and to screen and identify new targets for cancer therapeutics *in vitro* and *in vivo*.

ii. Organisation's role or significance in the overall research effort within the field of the Concept on both the national and international scales

Laboratory of Molecular Oncology: Research effort within the field is focused on cytotoxic and long-term antitumor effect of human engineered MSC against chemoresistant tumor cells and tumor initiating cells on experimental metastasis models. Furthermore, the aim is to find a novel therapeutic paradigm and/or combination for augmented therapy to target subpopulations of nondividing and chemoresistant tumor cells with properties of cancer stem cells. Our Laboratory has been and is the leading force in the field of mesenchymal stem cells and their potential in cancer therapy.

Laboratory of Molecular Genetics: The major part of the work has been and will be performed at the Laboratory of Molecular Genetics. The Laboratory of Molecular Genetics is the most significant laboratory in Slovakia dealing with the molecular nature of DNA repair mechanisms and their roles in mutagenesis and carcinogenesis with an intended impact on clinical practice and outcomes. Mentioned research outlines, ideas and strategies will also be solved in close multiple international collaborations (listed elsewhere).

Laboratory of Mutagenesis and Carcinogenesis: Laboratory of Mutagenesis and Carcinogenesis has a leading role in the field of mutagenesis and carcinogenesis and since 2008 also in nanotoxicology at the national level. In collaboration with colleagues from the former Laboratory of Molecular Biology, we shall extend our research into the field of molecular mechanism(s) of biological effects of nanoparticles.The scientific staff of the Laboratory organizes regularly the bilateral Czech-Slovakian workshops focused on actual problems in the field of genetic toxicology, nanotoxicology and cancer prevention. Laboratory offers services for other organisations and trains scientists/students interested in various methods generaly used in genetic toxicology. At the international level, Laboratory cooperates with various excellent laboratories (listed elsewhere).

Laboratory of Cancer Genetics: Research at the Laboratory of Cancer Genetics has a long history of determination of molecular genetics methods for identification of germline-mutation carriers in patients with hereditary forms of polyposis and non-polyposis colorectal cancers (FAP, Lynch syndrome – HNPCC), breast and ovarian cancers (HBOC). Results of these analyses have already been introduced into cancer patient

management. Furthermore, research at the Laboratory focuses on the impact of probiotic bacteria on prevention of several negative side effects of the chemotherapy treatment in paediatric patients (*e.g*. febrile neutropenia).

Laboratory of Tumor Immunology: The Laboratory is the leading force in establishing the flow-cytometry methods for studies of all aspects of cell viability, differentiation and phenotyping of various leukemias. More recently, the research topics have shifted towards the studies on modulation of cisplatin resistance by transcriptional or proteasome inhibition in human cancer cells; to new therapeutic approaches and prognostic markers in breast and ovarian malignancies; to the monitoring of several immunological parameters of multiple myeloma patients during BioBran consumption; to the effects of mineral realgar nanoparticles on human cancer cells in combinations with isothiocyanates; and to epigenetic regulation of HLA-G transcription in malignant hematopoetic cells from patients with AML and B-CLL.

iii. Objectives of the Concept

Laboratory of Molecular Oncology: We propose to target clinically relevant cell subpopulations (nondividing and chemoresistant) *via* purine nucleoside phosphorylase combined with fludarabine (a prodrug) as they might affect both the non-dividing qiuescent and the chemoresistant tumor cells. We suggest that antitumor treatment with engineered MSCs combined with other modalities may control the metastatic spread of chemoresistant tumor cells. Our therapeutic paradigm will be evaluated on primary human tumor samples and verified on small animal models as necessary prerequisite for potential future clinical exploitation.

Laboratory of Molecular Genetics: To better understand fundamental mechanisms of certain DNA repair pathways, we shall characterize the Srs2, Nej1 and Lif1 proteins in detail and examine their possible role in making the choice between the two major DSB repair pathways in *S. cerevisiae*, HR and NHEJ. Furthermore, we shall study the involvement of the ERCC3 protein and/or NER and/or TFIIH holocomplex in DDR, checkpoint signalling and apoptosis. In the project of the use of DNA repair knowledge in clinical practice, we plan to establish the analysis of DNA repair foci as a tool for assessment of susceptibility to childhood leukemia. Next, we shall estimate prevalence of leukemic gene fusions in Slovak population and provide unequivocal support for one of the models for etiology of leukemia which may result in an improved early diagnostics. We also plan to determine the effects of proton radiation on DNA damage, cell cycle changes, cell viability and apoptosis, as all this is crucial for the implementation of an innovative technology of intensity modulated proton therapy into clinical practice in Slovakia.

Laboratory of Mutagenesis and Carcinogenesis: The research activity of the Laboratory of Mutagenesis and Carcinogenesis will be a continuation of ongoing research devoted to i) molecular and cellular mechanisms of chemical carcinogenesis, including the regulation of gene expression in growth-arrested cells and apoptosis, ii) nanotoxicology with emphasis on magnetic nanoparticles as potential carries/vectors for targeted drug delivery into malignant tissue, iii) molecular and cellular mechanisms underlying the chemoprotective potential of natural substances of different origins aimed at the prevention of human health, and iv) combinatorial chemistry which has been emerged as a new technology for rapid synthesis of large number of compounds. The objectives of the research activity are to advance the understanding of cellular and molecular mechanisms underlying the process of neoplastic transformation in order to prevent and improve cancer treatment.

Laboratory of Cancer Genetics: In relation to previous experiences, we shall continue research on the molecular alterations in colorectal and breast cancer patients. We shall

also study the effects of epigenetic gene silencing, specifically the methylation of genes associated with invasiveness and metastasizing in breast cancer. We shall continue in our studies on the role of bacteria in cancer and AIDS.

Laboratory of Tumor Immunology: As a continuation of our previous research, we shall continue to use cell-based imaging methods to follow various aspects of detection, treatment and prognosis of cancer cells or patients. We shall extend our effort to human studies with the special focus to the role of immune system fitness in cancer survivals and in the field of tertiary prevention.

iv. Proposed strategies and methods to be applied, and time schedule

Laboratory of Molecular Oncology: Characterization of chemoresistant cells derived *in vitro* and *in vivo* from tumor cell lines, dissociated xenografts and human tumor samples (cell biology, immunophenotype, cancer stem cell properties) will be followed by MSC mediated treatment with/without augmentation on small animal model of experimental metastasis derived from human chemoresistant tumor cells lines and evaluated by non-invasive bioluminescent imaging.

Laboratory of Molecular Genetics: Mapping of interacting domains within the Lif1-Srs2 complex using the two-hybrid and pull-down assays. Studies on the assembly of Nej1-Srs2 and Lif1-Srs2 under condition of no Nej1-Lif1 interaction assessed by the same experimental approach as described above: 1) An impact of Nej1 and Lif1 on helicase activity of Srs2 monitored by DNA helicase assay *in vitro*, 2) Impact of Srs2 on DNA binding activity of Nej1 and Lif1 assayed using electrophoretic mobility shift assay, 3) Monitoring the impact of Lif1 on antirecombinogenic activity of Srs2 by measurement of the Rad51 filament disruption, 4) Determination of checkpoint activation through phosphorylation of Chk1 and p53 proteins, as well as 5) the stability of TFIIH by Western immunoblotting followed by flow cytometry to measure the cell cycle progression and apoptosis, 6) Screening of umbilical cord blood (UCB) for preleukemic clones/gene fusions by multiplex and real time PCR, 7) Analysis of dose responses and time kinetics for DNA repair foci, comets, chromosomal aberrations and apoptosis in cells from UCB with and without preleukemic clones, 8) Assesment of different proton beam energies on biological effects for potential clinical practice, 9) Determination of biomarkers 53BP1, ATM, NBS1 and γ-H2AX by immunostaining in situ, confocal laser scanning microscopy and Metafer system in patients undergoing local radiotherapy of breast cancer.

Laboratory of Mutagenesis and Carcinogenesis: A multidisciplinary approach to study the biological effects of nanoparticles. The approach includes preparation and characterization of specific magnetic nanoparticles (in collaboration with the Institute of Experimental Physics, Košice and Institute of Virology, Bratislava), studies of biological effects of these nanoparticles by standard and molecular biology methods (PCR, PCR-RFLP, DNA sequence, western-blotting, immunostaining and cytological technologies, qRT-PCR, flow cytometry, Image Stream, etc.). Further, the role of NF1/Smad4 in stress-induced regulation of gene expression will be studied. The role of NF1 in the expression of *p21* and *ANT2* will be studied by real time PCR, chromatin immunoprecipitation and co-immunoprecipitation.

Laboratory of Cancer Genetics: The next research projects will be focused on utilisation of cancer specific epigenetic features in patient management. In breast cancer patients we shall investigate relation between DNA methylation levels in selected genes for growth, invasiveness and metastasis regulation and the breast cancer aggressiveness. In the cancer cell line model we shall study the histone modification and DNA methylation interactions in transcription silencing of cancer associated genes. Further research projects will be focused on study of *APC* gene function in colorectal carcinogenesis in a mouse model APC^{+}/APC1638N. Deficiency of the mouse *APC* gene

function will be completed by application of recombinant bacteria bearing expression plasmid with the human *APC* gene. Potential reduction of intestinal tumors formation will be tested microscopically and immunohistochemically with polyclonal antibody against the APC protein. The study of the role of bacteria in cancer and AIDS will be continued by testing of throat swabs bacteria isolated from HIV positive children from Cambodia and Kena for expression of HIV sequences detected previously. The expression will be monitored by monoclonal antibodies against major HIV antigens.

Laboratory of Tumor Immunology: By biological, biochemical and immunological techniques, in human tumor sensitive- and multidrug resistant cells, leukemic, ovarian-, or breast carcinoma to determine the relevance of transcriptional/proteasomal regulation of drug resistance, and signaling/apoptotic pathway molecules, as molecular targets for the single- or combined *in vitro* chemotherapy. With the aid of flow cytometry, real-time PCR, biochemical and immunochemical methods, to evaluate anticancer effects of biological active natural compounds in the context of potential synergism in combination treatments with chemotherapeutics, as well as the use experimental therapeutic approaches, such as the use suicide gene therapy and nanosized particle drugs. To investigate potential immunotherapy in ovarian cancer cells by immune complexes of ovarian-specific anti-TAA (tumor-associated antigens), monoclonal antibodies and ovarian carcinoma cell lysates together with bacterial ghosts (BGs). To strengthen cooperation with clinical partners in research projects using well defined tumor sample collections to discriminate poor prognosis patients early in their course of disease (circulating tumor cells, exosomes, National Cancer Hospital, Bratislava).

III. Partial indicators of the main activities:

1. Research output

i. Principal forms of research outputs of the Organisation

Scientists from CRI SAS publish their results in peer-reviewed, impacted outstanding international or national scientific journals, monographs and books, and present their results at international and national symposiums, conferences and workshops in form of lectures or poster presentations. Beside the basic research, in line with the worldwide trends, part of the research activities of the Institute is devoted to translational cancer research. Results of the scientific outcome of the Institute represent basis for novel prospective diagnostic tools due to close collaboration of the Institute with the largest cancer hospitals in the Slovak Republic (National Cancer Institute and St. Elisabeth Cancer Institute). Scientists have been invited to present their results at international renowned conferences and meetings. In addition, the Institute is actively participating in the education and training of the undergraduated students (Master theses) and graduated students (Rigorous thesis) and the scientists give lectures at the Universities and supervise PhD theses. The Institute is accredited for teaching PhD students in two scientific programs, experimental oncology and genetics. Moreover, the Institute with cooperation with the Cancer Research Foundation (CRF) has initiated a special education project (Scientific Workshop – Oncology) focused on students at the secondary schools to explain them the science in general and cancer research, in particular in a comprehensible way.

ii. List of the selected publications documenting the most important results of basic research. Total number of publications in the whole assessed period should not exceed the average number of the research employees. The principal science outputs (max. 5) are in bold.

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iii. List of monographs/books published abroad

[1] BENICHOU, J. - BONIOL, C. - LAVECCHIA, F. – LEVI, P. - MAISONNEUVE, C. - MAZZETTA, A. - D°ONOFRIO, E. - PLESKO, I. - ČLEN, S. - PUKKALA, MJ. - QUINN, C., - ROBERTSON, D. - ZARIDZE, D. - ZATONSKI, W.: Atlas of cancer mortality in Europe. IARC, 2008, ISBN 159

[2] Microbes, viruses and parasites in AIDS process. Vladimír Zajac. Chorvátsko : InTech, 2011. ISBN 978-953-307-601-0. (Editor)

iv. List of monographs/books published in Slovakia

[1] TOMEK, D. - BIELIK, J. - CHALUPOVÁ, V. - KOZA, I. - ONDRUŠOVÁ, M. - BAŇASOVÁ, K. - ŠPÁNIK, S. - KAUŠITZ, J. - MARENČÁK, J. - MARDIAK, J. - FOLTÁN, V. - CHALUPA, I. - KOREŇ, B. - ŠÁLEK, T. - ŠUFLIARSKY, J. - OBŠITNÍK, B. - LESÁKOVÁ, V. - TÓTH, K. - HRMOVÁ, D. - VENCELOVÁ, M. - GLATZ, P.: Inovácie v systémovej liečbe vybraných onkologických ochorení. Med-In Alfa, 2007, ISBN 978-80-969659

v. List of other scientific outputs specifically important for the Organisation

[1] The Institute publishes periodically Scientific Reports in which the research activities of the Institute are summarized.

[2] The Institute publishes non-periodically publications addressed to students of the secondary schools to introduce the science in general and cancer research in particular in a comprehensible way.

[3] The website of the Institute has a domain where the general public can find information pertinent to cancer research.

vi. List of patents registered abroad, incl. revenues

[1] 0

vii. List of patents registered in Slovakia, incl. revenues

[1] 0

viii. Table of research outputs

*Table **Research outputs** shows research outputs in number of specified entries; these entries are then divided by FTE employees with a university degree (from Tab. Research staff) for all Organisation at the respective year; finally these entries are divided by the total salary budget (from Tab. Salary budget).*

Research outputs	2007			2008			2009			2010			2011			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	No. / FTE	No. / salary budget	number	averaged number per year	av. No. / FTE	av. No. / salary budget
chapters in monographs, books published abroad	2	0.036	2.58	0	0.000	0.00	0	0.000	0.00	1	0.020	1.20	2	0.048	2.50	5	1.0	0.019	1.23
chapters in monographs, books published in Slovakia	2	0.036	2.58	0	0.000	0.00	0	0.000	0.00	0	0.000	0.00	0	0.000	0.00	2	0.4	0.008	0.49
WOS publications	34	0.620	43.81	44	0.751	55.12	37	0.638	43.73	38	0.749	45.70	31	0.746	38.83	184	36.8	0.698	45.43
scientific publications indexed by other databases (specify)	0	0.000	0.00	0	0.000	0.00	0	0.000	0.00	1	0.020	1.20	0	0.000	0.00	1	0.2	0.004	0.25
scientific publications in other journals	8	0.146	10.31	3	0.051	3.76	2	0.034	2.36	8	0.158	9.62	3	0.072	3.76	24	4.8	0.091	5.93
publications in proc. of international scientific conferences	1	0.018	1.29	2	0.034	2.51	2	0.034	2.36	3	0.059	3.61	5	0.120	6.26	13	2.6	0.049	3.21
publications in proc. of nat. scientific conferences	2	0.036	2.58	2	0.034	2.51	6	0.103	7.09	4	0.079	4.81	1	0.024	1.25	15	3.0	0.057	3.70
active participations at international conferences	31	0.565	39.94	34	0.581	42.59	40	0.690	47.27	57	1.124	68.55	61	1.468	76.40	223	44.6	0.846	55.06
active participations at national conferences	23	0.419	29.64	30	0.512	37.58	11	0.190	13.00	4	0.079	4.81	4	0.096	5.01	72	14.4	0.273	17.78
patents registered in Slovakia	0	0.000	0.00	0	0.000	0.00	0	0.000	0.00	0	0.000	0.00	0	0.000	0.00	0	0.0	0.000	0.00
patents registered in abroad	0	0.000	0.00	0	0.000	0.00	0	0.000	0.00	0	0.000	0.00	0	0.000	0.00	0	0.0	0.000	0.00

ix. List of patents and patent applications

0

x. Supplementary information and/or comments on the scientific output of the Organisation

International importance of the research performed at CRI SAS is well documented by publications in very highly impacted Journals (*e.g. Nature, Blood, JAMA, Current Biology, PNAS, Cancer Research, Molecular Therapy*). Also, the citation index is increasing

rapidly. University students regularly apply for our undergraduate and PhD. programs. Our scientists are invited to give lectures as invited speakers at national and international conferences. Their scientific output is reflected by numerous prestigious grants and fellowship awards that allow them to further extend our cooperation with outstanding institutes and laboratories. Moreover, accepting their research qualities and knowledge, scientists from CRI SAS are asked to write a review articles for renowned scientitic journals about the topics of their research and are members of international scientific editorial boards. Last but not least to mention are the activities of the researchers as reviewers for many acknowledged journals and project applications which reflects the worldwide recognition of their expertise within their particular research area.

Although the National Cancer Registry (NCR) was founded by CRI SAS in the sixties of last century, based on decision of the Ministry of Health, NCR has been transferred to become an integral part of the National Centre for Health Information. This was not a good solution in terms of the fulfilling the aims of the international cooperation as the scientific activities are not covered in the mission of the NCHI. The epidemiological data collection on the numbers of oncological diseases itself does not suffice to hold our position in the international competition of oncological registries, where the Slovak Oncology Registry was regarded as one of the best in Europe.

Notice: List of all research outputs of monitored assessment period of structure of the Organisation's annual report is included in the separate annex

Annex 1 **List of publications in 2007, 2008, 2009, 2010, 2011**

Annex 2 **List of Citations in 2006, 2007, 2008, 2009, 2010**

Annex 3 **List of Presentations in 2007, 2008, 2009, 2010, 2011**

Annex 4 **List of 10 top cited publications and number of their citations**

2. Responses to the scientific output

*Table **Citations** shows specified responses to the scientific outputs; these entries are then divided by the FTE employees with a university degree (from Tab. Research staff) for all Organisation at the respective year; finally these entries are divided by the total salary budget (from Tab. Salary budget).*

Citations	2006			2007			2008			2009			2010			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	No. / FTE	No. / salary budget	number	averaged number per year	av. No. / FTE	av. No. / salary budget
Web of Science	513	9.4	661.0	497	8.5	622.6	647	11.2	764.6	636	12.5	764.9	599	14.4	750.2	2892	578.4	11.0	3570.0
SCOPUS (if not listed above)	89	1.6	114.7	216	3.7	270.6	161	2.8	190.3	191	3.8	229.7	235	5.7	294.3	892	178.4	3.4	1101.1
Google Scholar	12	0.2	15.5	5	0.1	6.3	6	0.1	7.1	7	0.1	8.4	2	0.0	2.5	32	6.4	0.1	39.5
in monographs, conf. proceedings and other publications abroad (if not listed above)	9	0.2	11.6	6	0.1	7.5	5	0.1	5.9	3	0.1	3.6	2	0.0	2.5	25	5.0	0.1	30.9
in monographs, conf. proceedings and other publications in Slovakia (if not listed above)	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0.0

i. List of 10 top-cited publications and number of their citations in the assessment period (2006 – 2010)

[1] WALSH, T. - CASADEI, S. - COATS, K. - SWISHER, E. - STRAY, S. - HIGGINS, J. - ROACH, K. - MANDELL, J. - LEE, M. - ČIERNIKOVÁ, S. - FORETOVA, L. - SOUCEK, P. - KING, M.: Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer. In **JAMA-Journal of the American Medical Association**. Vol. 295 no. 12 (2006), p. 1379-1388. (23.175-IF2006): **CITATIONS 198**

[2] METIVIER, R. - GALLAIS, R. - TIFFOCHE, C. - LE PÉRON, C. - JURKOWSKA, R. - CARMOUCHE, R. - IBBERSON, D. - BARÁTH, P. - DEMAY, F. - REID, G. - BENES, V. - JELTSCH, A. - GANNON, F. - SALBERT, G.: Cyclical DNA methylation of a transcriptionally active promoter. In **Nature**. Vol. 452 no. 7183 (2008), p. 45-50. (31.434-IF2008): **CITATION 178**

[3] LETAVAYOVÁ, L. - VLČKOVÁ, V. - BROZMANOVÁ, J.: Selenium: from cancer prevention to DNA damage. In **Toxicology**. Vol. 227 no. 1-2 (2006), p. 1-14. (2.685-IF2006): **CITATIONS 81**

[4] OVESNÁ, Z. - VACHÁLKOVÁ, A. - HORVÁTHOVÁ, K. - TÓTHOVÁ, D.: Pentacyclic triterpenoic acids: new chemoprotective compounds. In **Neoplasma**. Vol. 51 no. 5 (2004), p. 327-333. (0.822-IF2004): **CITATIONS 70**

[5] DUDÁŠ, A. - CHOVANEC, M.: DNA double-strand break by homologous recombination. In **Mutation research-Reviews in mutation research**. Vol. 566 no. 2 (2004), p. 131-167. (3.667-IF2004): **CITATIONS 57**

[6] ŠOLTÝSOVÁ, A. - ALTANEROVÁ, V. - ALTANER, Č.: Cancer stem cells. In **Neoplasma**. Vol. 52 no. (2005), p. 435-440. (0.731-IF2005): **CITATIONS 54**

[7] KUČEROVÁ, L. - ALTANEROVÁ, V. - MATÚŠKOVÁ, M. - TYČIAKOVÁ, S. - ALTANER, Č.: Adipose Tissue-Derived Human Mesenchymal Stem Cells Mediated Prodrug Cancer Gene therapy. In **Cancer research**. Vol. 67 no. 13 (2007), p. 6304-6313. (7.672-IF2007): **CITATIONS 48**

[8] JAKUBÍKOVÁ, J. - SEDLÁK, J. - MITHEN, R. - BAO, Y.: Role of PI3K/Akt and MEK/ERK signaling pathways in sulforaphane- and erucin-induced phase II enzymes and MRP2 transcription, G2/M arrest and cell death in Caco-2 cells. In **Biochemical pharmacology**. Vol. 69 no. 11 (2005), p. 1543-1552. (3.617-IF2005**): CITATIONS 45**

[9] JANTOVÁ, S. - ČIPÁK, Ľ. - ČERNÁKOVÁ, M. - KOŠŤÁLOVÁ, D.: Effect of berberine on proliferation, cell cycle and apoptosis in HeLa and L1210 cells.. In **Journal of pharmacy and pharmacology**. Vol. 55 no. 8 (2003), p. 1143-1149. (1.502-IF2003): **CITATIONS 41**

[10] BIES, J. - MARKUS, J. - WOLFF, L.: Covalent Attachment of the SUMO-1 Protein to the Negative Regulatory Domain of the c-Myb Transcription Factor Modifies Its Stability and Transactivation Capacity. In **Journal of Biological Chemistry**. Vol. 277 no. 11 (2002), p. 8999-9009. (6.696-IF2002): **CITATIONS 41**

ii. List of top-cited authors from the Organisation (at most 10 % of the research employees) and their number of citations in the assessment period (2006 – 2010)

[1] SLAMEŇOVÁ Darina, DSc.	SCI: **328**
[2] Assoc. Prof. ALTANER Čestmír, DSc.	SCI: **319**
[3] SEDLÁK Ján, DSc.	SCI: **303**
[4] CHOVANEC Miroslav, PhD.	SCI: **284**
[5] BARÁTH Peter, PhD.	SCI: **243**

iii. Supplementary information and/or comments on responses to the scientific output of the Organisation

Considering the leading role of CRI SAS in Slovak oncological research, our scientists are invited to participate in large international studies (*e.g.* to achieve the most relevant picture of "founder" effects in hereditary types of cancer). The analysis of 5226dupC mutation and its frequency in Europe was performed in collaboration with cancer centres in Greece, Czech Republic, France, Russia, Poland, Denmark and Latvia. These collaborations have already brought the results published at prestigous international journals.

Many researchers from CRI SAS are members of the scientific advisory board in international journal Neoplasma and contribute to the evaluation process with scientific advice and active participation to revision process which further helps to constantly increase its impact factor. It is very important to mention the activities of the researchers as reviewers for many acknowledged journals which reflect the worldwide recognition of their expertise within their particular research area. Both publication activity and the citation indexes in combination reveal the significance of their work within the specific research field. Moreover, distinguished scientific output of the researchers also contributed to their numerous invitations to join the cooperation project proposals and international consortia. The invitation for the membership in International Consortia for Cell Therapy and Immunotherapy serves as one of the many examples.

3. Research status of the Organisation in the international and national context

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

[1] List of the most important research activities documenting international importance of the research performed by the Organisation, incl. major projects (details of projects should be supplied under Indicator 4). Collective membership in the international research organisations, in particular within the European Research Area

[1] CRI SAS is a permanent member of the prestigious Organization of the European Cancer Institutes (**OECI**)

[2] CRI SAS cooperates with several reputable international organizations including *International Agency for Research on Cancer* (**IACR**), *Union for International Cancer Control* (**UICC**) and *World Health Organization* (**WHO**).

[3] Scientists of the Institute are members of various international scientific organizations including the *European Association for Cancer Research* (**EACR**), *European Environmental Mutagen Society* (**EEMS**), *Federation of European Biochemical Society* (**FEBS**), *International Association of Cancer Registries* (**IACR**)*, International Society of Analytical Cytology (***ISAC***), American Association for Cancer Research* (**AACR**), *International Society for Gastrointestinal Hereditary Tumours* (**ISGHT**) *American Society for Biochemistry and Molecular Biology* (**ASBMB**), *Czecoslovak Biolocal Society* (**CSBS**) and *Genetic Society of Gregor Mendel* (**GSGM**).

[4] Scientists of the Institute were/are members of the scientific boards of international research programs: *International Association for the promotion of cooperation with scientists from the independent states of the former Soviet Union* (**INTAS**), *European School of Oncology* (**ESO**), *International Association for Comparative Research on Leukemia and Related Diseases* (**IACRLRD**)

[5] Some scientists of the Institute were/are representatives of the Slovak Republic in the European Organizations: i) *European Survey on Bio-medical Research Infrastructures*, (**Bio-med RI**), ii) *European Cancer Research Managers Forum* (**ECRMF**, FP6), iii) the Standing Committee *of the European Medical Research Councils* (**EMRC**) and consortium of EU-funded FP7 project *ERA-NET on Translational Cancer Research* (**Transcan**,),

[6] Scientists of the Institute are members of the international scientific editorial boards (*Viral Immunology*; *Journal of Experimental and Clinical Cancer Research; International Journal of Medicine, Biology and Environment*; *Experimental Pathology and Parasitology*; *Folia Biologica*; *Nowotwory*)

[7] Scientists of the Institute have been awarded various prestigious international grants (*ICRETT, EMBO, FEBS, AACR-NCI International Investigator Opportunity grant 2007, Maria Curie Felowship, National Cancer Institute (NCI), Bethesda, USA Fellowship, etc*.) that allow them to work at various outstanding Laboratories over the Europe and USA.

[8] Scientists of the Institute have participated in various international and multilateral projects (FP6, FP7, EUROCHIP-2, Atlas of Cancer Mortality in Europe, GLOBOCAN, ACCIS Programme, European Cancer Incidence project).

[9] Some scientist of the Institute have evaluated international projects funded by Genesis Oncology Trust, New Zealand; Israel Science Foundation; Samatha Dickson Brain Tumour Trust Great Britain; Swiss National Science Foundation;

[10] Scientists of the Institute collaborate with numerous national and international Institutes and Laboratories over the world; herewith contribute substantially to strengthen the European Research Area.

[2] List of international conferences (co-) organised by the Organisation

[1] Genomics and Proteomics of Cancer, INYS (International Networking for Young Scientists), February 28 – March 2, 2007, Smolenice, Slovakia (CRI SAS was the co-organizer of the meeting)

[2] Synthetic and Natural Compounds in Cancer Therapy and Prevention, March 28 – 30, 2007, Bratislava, Slovakia (CRI SAS was the co-organizer of the conference)

[3] 5th DNA Repair Workshop, May 25 – 29, 2008, Smolenice Castle, Slovakia (CRI SAS was the organizer of the conference

[4] Drug Resistance in Cancer, June 7- 11, 2008, Smolenice Castle, Slovakia (CRI SAS was the co-organizer of the meeting

[5] Natural Compounds in Cancer Prevention and Treatment, October 13 – 15, 2009, Smolenice Castle, Slovakia (CRI SAS was the co-organizer of the meeting)

[6] EU-USA DNA Repair Workshop: Dynamics of DNA Repair Enzymes Involved in Nucleotide Excision Repair and Inter-Strand Crosslinks Repair: From Molecules to Man, May 23 – 27, 2010, Smolenice Castle, Slovakia (CRI SAS was the organizer of the conference)

[7] Central European Meeting on Genome Stability and Dynamics, May 13, 2011, Bratislaava, Slovakia (CRI SAS was the co-organizer of the meeting)

[8] 2nd Drug Resistance in Cancer, May 29 – June 1, 2011, Smolenice Castle, Slovakia (CRI SAS was the organizer of the conference)

[3] List of journals edited/published by the Organisation:

1. **WOS (IF of journals in each year of the monitoring period)**

Neoplasma

IF 2006: **1.247**

IF 2007: **1.208**

IF 2008: **1.179**

IF 2009: **1.192**

IF 2010: **1.449**

2. not included in the databases:

[1]Cancer in the Eye of Scientists, ISBN 978-80-970058-9-4, published in 2008

[2] Scientific report 2007 – 2009, ISBN 978-80-970128-3-0, published in 2010

[3] Scientific Report 2006 – 2010, ISBN 978-80-970128-6-1, published in 2011

[4] List of edited proceedings from international scientific conferences and other proceedings

[1] Genomics and Proteomics of Cancer, INYS (International Networking for Young Scientists), Book of Abstracts, Smolenice Castle, Slovakia, Cancer Research Institute, 2007

[2] Synthetic and Natural Compounds in Cancer Therapy and Prevention, Book of Abstracts, March 28 – 30, 2007, Bratislava, Slovakia, ISBN 978-80-969663-2-5

[3] 5th DNA Repair Workshop, Book of Abstracts, Bratislava, Cancer Research Institute, 2008, ISBN 978-80-739941-7-4

[4] Drug Resistance in Cancer, Book of Abstracts, June 7 - 11, 2008, Smolenice Castle, Slovakia, ISBN 978-80-969951-2-7

[5] Natural Compounds in Cancer Prevention and Treatment, Book of Abstracts. Bratislava, Cancer Research Institute and Cancer Research Foundation, 2009. ISBN 978-80-970128-2-3.

[6] EU-US DNA Repair Workshop. Book of Abstracts, Bratislava, Cancer Research Institute, 2010, ISBN 978-80-7399-954-4

[7] 2nd Drug Resistance in Cancer, Book of Abstracts, Albert Breier, Ján Sedlák (Eds.), Cancer Research Institute and Institute of Molecular Physiology and Genetics, 2011, ISBN 978-80-970128-4-7

- **National position of the Organisation**

i. List of selected most important national projects (the EU Structural Funds, Slovak Research and Development Agency (APVV), State Research Programmes, Scientific Grant Agency of the Slovak Academy of Sciences and the Ministry of Education (VEGA), Centres of Excellence, National Reference Laboratories and others)

EU Structural Funds

[1] Centre of Excellence for Translational Research in Molecular Medicine

[2] Centre of Excellence for Translational Research in Molecular Medicine 2

[3] Diagnostics of Socially Important Disorders in Slovakia, based on Modern Biotechnologies

[4] Implementation of Radiobiological Research of Intensity-Modulated Proton Therapy into Clinical Oncology

[5] Establishment of the Competence Centre for Research and Development in the Field of Molecular Medicine

Slovak Research and Development Agency (APVV)

[1] Epithelial-mesenchymal transition in the model of breast carcinoma stem cells *in vitro*

[2] Further *in vivo* characterisation of the mutant and polymorphic DNA ligase IV proteins found in LIG4 patients

[3] Plant extracts – anti-inflammatory, cytotoxic and antimutagenic effects in animals

[4] Participation of the central nervous system in monitoring and modulation of tumorigenesis. New approach for the study of cancer etiopathogenesis

[5] Human mesenchymal stem cells as cytoreagents for metastasis-targeted therapy

[6] XPB/XPD DNA helicases: structure-function studies and a role in apoptosis

[7] Intestinal bacteria in ethiology of colorectal carcinoma and immunodeficiency aquired syndrome

[8] Hypericum spp. as a source of bioactive compounds with antitumor activity

[9] Centre for Signalosome Research[10] Assessment of spontaneous mutagenesis in yeast cells expressing the human DNA ligase proteins found in LIG4 patients

[10] DNA Repair and Preleukemic Clones in Cord Blood Stem Cells

[11] Identification of predictive epigenetic biomarkers in breast cancers

[12] Regulation of DNA double-strand repair mechanism choice

[13] Neurobiology of Cancer. The Study of the Nervous System Role in Etiopathogenesis of Tumor Growth and Development of Metastasis

[14] Hypericin: Biotechnology, Signalome, Phytodynamic Therapy

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

[1] Chemotherapy, multidrug resistance (MDR) its modulation and relationship of these events to programmed cell death (apoptosis) in human tumor cells

[2] A role of the ERCC3 DNA helicase in DNA repair and apoptosis

[3] DNA protective agents available in cancer research

[4] The study of normal and leukemia hematopoietic populations as a basis to discriminate between leukemia and regenerating cells

[5] Interaction of Human Adipose-tissue Derived Mesenchymal Stem Cells with Human Cancer Cells

[6] Cytogenetic monitoring of the cervical cancer patients responses to radiation; prediction of the radiotherapy success

[7] Yeast *K.lactis* as a tool for study the mechanism of Bax induced cytotoxicity: A role for actin-binding proteins and lactate metabolism

[8] DNA methylation in hereditary and sporadic colorectal carcinomas with mismatch repair defect

[9] Integration of nuclear factor-1 (NF-1) into existing signaling pathways leading to growth-arrest

[10] The role and the contribution of *Escherichia coli* and *Schizosaccharomyces pombe* alkyltransferase homologues in the repair of DNA alkylation damage in yeast Saccharomyces cerevisiae

[11] Soluble non-classical HLA class I antigens

[12] Effect of natural compounds isothiocyanates (ITCs) on cellular mechanisms and markers associated with aggressive phenotype and treatment responsiveness in breast and ovarian cancer

[13] The role of genetic, epigenetic and phenotypic markers of the *MDR1* gene and protein for the prognosis and treatment of the acute myeloid leukemia

[14] Biological effect of newly discovered *RET* gene mutation in connection with multiple endocrinne neoplasia type 2

[15] Study of genetic and non-genetic factors participated in induction of familial adenomatous polyposis (FAP) and sporadic form of colon cancer

[16] Molecular markers for prediction of individual radiosensitivity in cancer therapy

[17] Study of essential oils and their components from the point of view of the protective action in the initiation step of carcinogenesis; experimental systems *in vitro* and *ex vivo*

[18] Molecular mechanisms of Inter-Strand Crosslinks Repair in *Saccharomyces cerevisiae*

[19] Identification of alternative protein partners of tumor suppressors from INK4 family

[20] Gene-cell therapy of cancer using a selfinactivating - retroviral vectors inducibly expressing tumour necrosis factor alpha in human mesenchymal stem cells

Centres of Excellence

[1] Centre for Signalome Research

[2] Centre of Excellence for study of metabolic aspects from the point of development, diagnosis and therapy of cancer

European Social Funds

[1] Innovative Program focused on Education of Young Experts in Oncology

ii. List of national scientific conferences (co)-organised by the Organisation

[1] Genetic Toxicology and Cancer Prevention, Bratislava, October 22 – 24, 2007 (CRI SAS was organizer of the conference)

[2] XLIV. Bratislavské onkologické dni, Sekcia experimentálna onkológia, (XLIV. Bratislavian Oncological Days; Section: Experimental oncology), Bratislava, October 3 - 5, 2007 (CRI SAS was co-organizer of the conference)

[3] Súťaž Mladý onkológov 2008 (Young Oncologists Competition), March 7, 2008, Bratislava (CRI SAS was co-organizer of the conference)

[4] Genetic Toxicology and Cancer Prevention, Bratislava October 13 – 15, 2008 (CRI SAS was organizer of the conference)

[5] XLV. Bratislavské onkologické dni, Sekcia expreimentálna onkológia, (XLV. Bratislavian Oncological Days; Section: Experimental oncology), Bratislava, October 1 -3, 2008 (CRI SAS was co-organizer of the conference)

[6] Achievements and Perspectives in Cancer Research in the Slovak Republic, March 6, 2009, Bratislava (CRI SAS was organizer of the conference)

[7] Genetic Toxicology and Cancer Prevention, Bratislava, October 12 – 14, 2009 (CRI SAS was organizer of the conference)

[8] XLVI. Bratislavské onkologické dni, Sekcia experimentálna onkológia, (XLVI. Oncological Days; Section: Experimental oncology), Bratislava, October 1 -2, 2009 (CRI SAS was co-organizer of the conference)

[9] Súťaž Mladý onkológ (Young Oncologist Competition), March 10, 2010, Bratislava (CRI SAS was co-organizer of the conference)

[10] XLVII. Bratislavské onkologické dni, Sekcia experimentálna onkológia, (XLVII. Bratislavian Bratislavian Oncological Days; Section: Experimental oncology), Bratislava, September 23 – 24, 2010 (CRI SAS was co-organizer of the conference)

[11] Probiotiká v onkológii (Probiotics in Oncology), Bratislava, March 7, 2011 (CRI SAS was organizer of the conference)

[12] Genetic Toxicology and Cancer Prevention, Bratislava, June 13 – 15, 2011 (CRI SAS was the organizer of the conference)

[13] XLVIII. Bratislavské onkologické dni, Sekcia experimentálna onkológia, (XLVIII. Bratislavian Bratislavian Oncological Days; Section: Experimental oncology), Bratislava, October 6 – 7, 2011 (CRI SAS was co-organizer of the conference)

iii. List of edited proceedings of national scientific conferences/events

[1] Genetic Toxicology and Cancer Prevention, Book of Abstracts, Bratislava, Cancer Research Institute, 2007, ISBN 978-80-969680-4-6

[2] Book of Abstracts from 8th International symposium about the History of medicine, pharmacy and veterinary medicine. Bujalková, M.- Pavlíková, Ľ. (Eds.). Martin: Jessenius Medical faculty of Comenius University et al., 2007. ISBN 978-80-88866-44-2.

[3] Genetic Toxicology and Cancer Prevention, Book of Abstracts, Bratislava, Cancer Research Institute, 2008, ISBN 978-80-970017-5-9

[4] Úspechy a perspektívy onkologického výskumu na Slovensku (Achievements and Perspective of the Cancer Research in Slovakia), March 7, Cancer Research Day, Alena Gábelová, Ján Sedlák. (Eds.), Bratislava, Cancer Research Institute, 2009. 118 s. ISBN 978-80-970128-0-9.

[5] Genetic Toxicology and Cancer Prevention, Book of Abstracts, Bratislava, Cancer Research Institute 2009, ISBN 978-80-970128-1-6

[6] Súťaž mladých onkológov (Young Oncologists Competition), Book of Abstracts. Bratislava: Cancer Research Foundation and Cancer Research Institute, 2010. ISBN 978-80-970403-6-9

[7] Probiotiká v onkológii (Probiotics in Oncology), Book of Abstracts, [electronic], Bratislava, Cancer Research Foundation and Cancer Research Institute 2011, ISBN 978-80-970128-5-4.

- **International/European position of the individual researchers**

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

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ii. List of employees who served as members of the organising and/or programme committees for international conferences

[1] Slameňová Darina, DSc. – member of the Scientific Program Committee of the conference: Synthetic and Natural Compounds in Cancer Therapy and Prevention, Bratislava, March 28-30, 2007

[2] Horváthová Eva, PhD. – member of the Organizing Committee of the conference: Synthetic and Natural Compounds in Cancer Therapy and Prevention, Bratislava, March 28-30, 2007

[3] Luciaková Katarína, DSc. – Coordinator of the INYS workshop, Smolenice Castle, February 28 – March 2, 2007

[4] Horváthová Eva, PhD. – tutor of the INYS workshop, Smolenice Castle, February 28 – March 2, 2007

[5] Piršel Miroslav, PhD. – President of the Scientific Program Committee and chairperson of the Organizing Committee of the conference: 5th DNA Repair Workshop, Smolenice Castle, May 25 – 29, 2008

[6] Dudáš Andrej, PhD. – member of the Organizing Committee of the conference: 5th DNA Repair Workshop, Smolenice Castle, May 25 – 29, 2008

[7] Kleibl Karol, PhD. – member of the Organizing Committee of the conference: 5th DNA Repair Workshop, Smolenice Castle, May 25 – 29, 2008

[8] Chovanec Miroslav, PhD. – member of the Scientific Program and Organizing Committee of the conference: 5th DNA Repair Workshop, Smolenice Castle, May 25 – 29, 2008

[9] Bartošová Zdena, PhD. – member of the Organizing Committee of the conference: Drug Resistance in Cancer, Smolenice Castle, June 7- 11, 2008

[10] Duraj Jozef, PhD. – member of the Organizing Committee of the conference: Drug Resistance in Cancer, Smolenice Castle, June 7- 11, 2008

[11] Sedlák Ján, DSc. – member of the Scientific Program and Organizing Committee of the conference: Drug Resistance in Cancer, Smolenice Castle, June 7- 11, 2008

[12] Sedlák Ján, DSc. – member of the Scientific Program Committee of the conference: Natural Compounds in Cancer Prevention and Treatment, Smolenice Castle, October 13 – 15, 2009

[13] Piršel Miroslav, PhD. – President of the Scientific Program Committee of the conference Dynamics of DNA Repair Enzymes Involved in Nucleotide Excision

Repair and Inter-Strand Crosslink Repair: From Molecules to Man, Smolenice Castle May 23 – 27, 2010

iii. List of employees who served as members of important international scientific bodies (e.g. boards, committees, editorial boards of scientific journals)

[1] Assoc. Prof. Altaner Čestmír, DSc. – member of Scientific Council of EU Program INTAS

[2] Assoc. Prof. Altaner Čestmír, DSc. – national representative in the EU program Bio-med RI

[3] Assoc. Prof. Altaner Čestmír, DSc. – member of European Cancer Research Managers Forum (ECRM)

[4] Assoc. Prof. Altaner Čestmír, DSc. – member of World Committee International Association for Comparative Research on Leukemia and Related Diseases (IACRLRD)

[5] Assoc. Prof. Altaner Čestmír, DSc. – member of the Scientific Council of European School of Oncology (ESO)

[6] Assoc. Prof. Altaner Čestmír, DSc. – expert for Cancer Research Strategy, Ministry of Health and Ministry of Education in Czech Republic

[7] Assoc. Prof. Altaner Čestmír, DSc. – National representative of Slovak Cancer Centre in Organization of European Cancer Institutes (OECI)

[8] Assoc. Prof. Altaner Čestmír, DSc. – member of editorial board of scientific journal Viral Immunology, USA;

[9] Assoc. Prof. Altaner Čestmír, DSc. – member of editorial board of scientific journal Journal of Experimental and Clinical Cancer Research, Italy

[10] Assoc. Prof. Altaner Čestmír, DSc. – member of editorial board of scientific journal Experimental Pathology and Parasitology, Bulgaria

[11] Assoc. Prof. Altaner Čestmír, DSc. – member of editorial board of scientific journal Folica Biologica, Prague, Czech Republic

[12] Assoc. Prof. Altaner Čestmír, DSc. – member of editorial board of scientific journal Nowotwory, Poland

[13] Poláková Katarína, DSc. – Member of Standing Commitee of European Medical Research Council (EMRC), European Science Foundation

[14] Assoc. Prof. Pleško Ivan, DSc. – Honorary Member of International Association of Cancer Registries

[15] Gábelová Alena, PhD. – national representative in the EU-funded ERA-NET on Translation Research Project

[16] Babušíková Oľga, MD, DSc. – member of editorial board of scientific journal Clincal Oncology, Czech republic

[17] Babušíková Oľga, MD, DSc. – member of editorial board of scientific journal Leukemia Research and Treatment

[18] Assoc. Prof. Novotný Ladislav, MD., DSc. – member of the editorial board of the scientific journal Medical Principles and Practice, Kuwajt

[19] Ujházy Viliam, MD., DSc. – member of the editorial board of the scientific journal Clinical Oncology, Czech Republic

[20] Assoc Prof. Zajac Vladimír, PhD. – member of the editorial board of the scientific journal Hereditary Cancer in Clinical Practice

[21] Ondrušová Martina, MD., PhD. – member of the editorial board of the scientific journal Clinical Oncology, Czech Republic

[22] Assoc. prof. Belyaev Igor, DSc. – member of editorial board of scientific journal Electromagnetic biology and Medicine

[23] Assoc. prof. Belyaev Igor, DSc. – member of editorial board of scientific journal International Dental and Medical Disorders

[24] Assoc. prof. Belyaev Igor, DSc. – member of editorial board of scientific journal ISRN Biophysics

[25] Assoc. prof. Belyaev Igor, DSc. – expert of Health systems and products, Risk assessment, HEALTH AND CONSUMERS DIRECTORATE-GENERAL, EUROPEAN COMMISSION

[26] Assoc. prof. Belyaev Igor, DSc. – member of Working group of the International Agency on Research in Cancer

[27] Assoc. prof. Belyaev Igor, DSc. – member of Russian National Committee on Non-Ionizing Radiation Protection

[28] Assoc. prof. Belyaev Igor, DSc. – member of Memorial Fund Committee of the Bioelectromagnetics Society

[29] Assoc. prof. Belyaev Igor, DSc. – member of editorial board of scientific journal

[30] Hunáková Ľuba, PhD. – member of the editorial board of the scientific journal ISRN Oncology

[31] Luciaková Katarína, DSc. – member of the editorial board of the scientific journal The Scientific World JOURNAL

iv. List of international scientific awards and distinctions

[1] Čipák Ľuboš, PhD. – ICRETT Fellowship

[2] Čipák Ľuboš, PhD. – EMBO Short Term Fellowship

[3] Čipák Ľuboš, PhD. – FEBS Short Term Fellowship

[4] Dudáš Andrej, PhD. – FWF Lise Meitner Program M1145

[5] Kučerová Lucia, PhD. – Travel award from 23rd IACRLRD Symposium, Germany, 2007

[6] Kučerová Lucia, PhD. – AACR-NCI International Investigator Opportunity grant 2007

[7] Kučerová Lucia, PhD. - Travel award to attend 3rd Berder Workshop on Tumor Microenvironment, 2009

[8] Kučerová Lucia, PhD. – Molecular Oncology Fellowship to attend FEBS Advanced Course on Translational Cancer Research, 2011

[9] Maršálková Lenka, MSc. – Certificate of Compliance, EUROTOX Basic Toxicology Course,

[10] Mészárosová Monika, MSc. – Certificate of Compliance, EUROTOX Basic Toxicology Course

[11] Srančíková Annamária, MSc. – Certificate of Compliance, EUROTOX Basic Toxicology Course

[12] Matúšková Miroslava, PhD. – Award for the best poster in the Biomedical Research Section, Central European Congress of Life Sciences EUROBIOTECH 2008, Krakow, Poland

[13] Matúšková Miroslava, PhD. – Young Scientist Award (2nd prize), 3rd Meeting FIRST (Forum of Italian Researchers on Mesenchymal Stromal Stem Cells), 2009, Milan, Italy

[14] Matúšková Miroslava, PhD. – Travel award to attend 5th Berder Workshop on Tumor Hypoxia and Angiogenesis, 2011

[15] Dudášová Zuzana, PhD. – British Council Fellowship

[16] Gurský Ján, MSc. – British Council Fellowship

[17] Valovičová Zuzana, MSc. – British Council Fellowship

[18] Rybanská Ivana, PhD. – British Council Fellowship

[19] Čierniková Soňa, PhD. – British Council Fellowship

[20] Vigašová Dana, MSc.. – EMBO Short-Term Fellowship

[21] Valovičová Zuzana, MSc. – DNA Repair Worksho 2008 Fellowship

[22] Gurský Ján, MSc. – Genome Stability Network Fellowship

[23] Horváthová Eva, PhD. – ICRETT Fellowship (2007)

[24] Horváthová Eva, PhD. – ICRETT Fellowship (2008)

[25] Fridrichová Ivana, PhD. – Ferring Pharmaceutical SA Travel Fellowship

Post-doctoral Positions

[26] Markus Ján, PhD. – National Cancer Institute, National Institute of Health, Bethesda, MD, USA

[27] Jakubíková Jana, PhD. – Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

[28] Boďo Juraj, PhD. – Institute of Pathology and Laboratory Medicine, Cleveland Clinic, Cleveland, OH, USA

[29] Šramko Marek, PhD. – National Cancer Institute, National Institute of Health, Bethesda, MD, USA

[30] Šramková Monika, PhD. – National Cancer Institute, National Institute of Health, Bethesda, MD, USA

[31] Rybanská Ivana, PhD. – National Institute of Ageing, National Institute of Health, Baltimore, MD, USA

[32] Košťanová-Poliaková Daniela, PhD. – The Research Institute of Molecular Pothology (IMP), Vienna, Austria

[33] Dudáš Andrej, PhD. – Max F. Perutz Laboratories, University of Vienna, Vienna, Austria

[34] Čipák Ľuboš, PhD. – University of Vienna, Vienna, Austria

v. List of employees with the highest H – index indicating field of science by WOS

The H – index values are without autocitations.

[1] Assoc. Prof. Altaner Čestmír, DSc. – 13

[2] Slameňová Darina, DSc. – 13

[3] Čipál Ľuboš, PhD. – 12

[4] Altanerová Veronika, PhD. – 11

[5] Sedlák Ján, DSc. – 14

[6] Horváthová Eva, PhD. – 12

[7] Jakubíková Jana, PhD. – 12

[8] Gábelová Alena, PhD. – 10

[9] Škorvaga Milan, PhD. – 10

[10] Frecer Vladimír, PhD. – 10

[11] Bies Juraj, DSc. – 14

[12] Hunáková Ľuba, PhD. – 10

[13] Luciaková Katarína, DSc. – 13

[14] Assoc. prof. Pleško Ivan, DSc. – 19

[15] Assoc. Prof. Belyaev Igor, DSc. – 13

- **National position of the individual researchers**

i. List of invited/keynote presentations at national conferences documented by an invitation letter or programme

0

ii. List of employees who served as members of organising and programme committees of national conferences

[1] Gábelová Alena, PhD. – President of the Scientific Program Committee of the conference Genetic Toxicology and Cancer Prevention, Bratislava, 2007

[2] Chalupa Ivan, PhD., – member of the Scientific Program Committee of the conference Genetic Toxicology and Cancer Prevention, Bratislava, 2007

[3] Slameňová Darina, DSc. – member of the Scientific Program Committee of the conference Genetic Toxicology and Cancer Prevention, Bratislava, 2007

[4] Gurská Soňa, PhD. – member of the Scientific Program Committee of the conference Genetic Toxicology and Cancer Prevention, Bratislava, 2007

[5] Valovičová Zuzana, PhD. – Chairperson of the Organizing Committee of the conference Genetic Toxicology and Cancer Prevention, Bratislava, 2007

[6] Maršálková Lenka, MSc. – member of the Organizing Committee of the conference Genetic Toxicology and Cancer Prevention, Bratislava, 2007

[7] Mészárosová M., MSc. – member of the Organizing Committee of the conference Genetic Toxicology and Cancer Prevention, Bratislava, 2007

[8] Horváthová Eva, PhD. – member of the Organizing Committee of the conference Genetic Toxicology and Cancer Prevention, Bratislava, 2007

[9] Altaner Čestmír, DSc. – member of the Scientific Program Committee of the conference: XLIV Bratislavian Oncological Days, Bratislava, 2007

[10] Babušíková Oľga, DSc. – member of the Scientific Program Committee of the conference: XLIV. Bratislavian Oncological Days, Bratislava, 2007

[11] Sedlák Ján, DSc. – member of the Scientific Program Committee of the conference: XLIV. Bratislavian Oncological Days, Bratislava, 2007

[12] Babušíková Oľga, DSc. – coordinator of the section: Anti-tumor immunity, at the XXIV. Meeting of the Czech and Slovak Alergologists and Clinical Immunologists, Prague, 2008

[13] Klobušická Margita, PhD. – co-organiser of the Young Oncologists Competition, March 7, 2008, Bratislava

[14] Sedlák Ján, DSc. – co-organiser of the Young Oncologists Competition, Bratislava 2008

[15] Gábelová Alena, PhD. – President of the Scientific Committee of the conference Genetic Toxicology and Cancer Prevention, Bratislava, 2008

[16] Chalupa Ivan, PhD. – member of the Scientific Committee of the conference Genetic Toxicology and Cancer Prevention, Bratislava, 2008

[17] Piršel Miroslav, PhD. – member of the Scientific Committee of the conference: History, Presence and Perspectives of Genetics, Bratislava, 2008

[18] Horváthová Eva, PhD. – member of the Organizing Committee of the 13th Interdisciplinary Toxicology Conference TOXCON 2008, Trenčianske Teplice, 2008

[19] Horváthová Eva, PhD. – member of the Organizing Committee of the conference Genetic Toxicology and Cancer Prevention, Bratislava, 2008

[20] Mészárosová Monika, MSc. – member of the Organizing Committee of the conference Genetic Toxicology and Cancer Prevention, Bratislava, 2008

[21] Valovičová Zuzana, PhD. – chairperson of the Organizing Committee of the conference Genetic Toxicology and Cancer Prevention, Bratislava, 2008

[22] Slameňová Darina, DSc. – member of the Scientific Program and Organizing Committee of the conference Genetic Toxicology and Cancer Prevention, Bratislava, 2008

[23] Altaner Čestmír, DSc. – member of the Scientific Program Committee of the conference: XLV. Bratislavian Oncological Days, Bratislava, 2008

[24] Babušíková Oľga, DSc. – member of the Scientific Program Committee of the conference: XLV. Bratislavian Oncological Days, Bratislava, 2008

[25] Sedlák Ján, DSc. – member of the Scientific Program Committee of the conference: XLV. Bratislavian Oncological Days, Bratislava, 2008

[26] Gábelová Alena, PhD. – chairperson of the Organising Committee of the conference: Achievements and Perspectives in Cancer Research in Slovakia, 2009, Bratislava

[27] Gábelová Alena, PhD. – President of the Scientific Program Committee of the conference Genetic Toxicology and Cancer Prevention, Bratislava, 2009

[28] Horváthová Eva, PhD. – member of the Organizing Committee of the conference Genetic Toxicology and Cancer Prevention, Bratislava, 2009

[29] Mesárošová Monika, MSc. – member of the Organizing Committee of the conference Genetic Toxicology and Cancer Prevention, Bratislava, 2009

[30] Valovičová Zuzana, PhD. – chairperson of the Organizing Committee of the conference Genetic Toxicology and Cancer Prevention, Bratislava, 2009

[31] Slameňová Darina, DSc. – member of the Scientific Program and Organizing Committee of the conference Genetic Toxicology and Cancer Prevention, Bratislava, 2009

[32] Chalupa Ivan, PhD. – member of the Scientific Program and Organizing Committee of the conference Genetic Toxicology and Cancer Prevention, Bratislava, 2009

[33] Altaner Čestmír, DSc. – member of the Scientific Program Committee of the conference: XLVI. Bratislavian Oncological Days, Bratislava, 2009

[34] Babušíková Oľga, DSc. – member of the Scientific Program Committee of the conference: XLVI. Bratislavian Oncological Days, Bratislava, 2009

[35] Sedlák Ján, DSc. – member of the Scientific Program Committee of the conference: XLVI. Bratislavian Oncological Days, Bratislava, 2009

[36] Klobušická Margita, PhD. – co-organiser of the Young Oncologists Competition, March 10, 2010, Bratislava

[37] Sedlák Ján, DSc. – co-organiser of the Young Oncologists Competition, March 10, 2010, Bratislava

[38] Sedlák Ján, DSc. – member of the Scientific Program Committee of the conference: XLVII. Bratislavian Oncological Days, Bratislava, 2010

[39] Gábelová Alena, PhD. – President of the Scientific Program Committee of the conference Genetic Toxicology and Cancer Prevention, Bratislava, 2011

[40] Slameňová Darina, DSc. – member of the Scientific Program and Organizing Committee of the conference Genetic Toxicology and Cancer Prevention, Bratislava, 2011

[41] Kozics Katarína, PhD. – chairperson of the Organizing Committee of the conference Genetic Toxicology and Cancer Prevention, Bratislava, 2011

[42] Mesárošová Minika, MSc. – member of the conference Genetic Toxicology and Cancer Prevention, Bratislava, 2011

[43] Regendová Eva, MSc. – member of the conference Genetic Toxicology and Cancer Prevention, Bratislava, 2011

[44] Horváthová Eva, PhD. – member of the conference Genetic Toxicology and Cancer Prevention, Bratislava, 2011

[45] Sedlák Ján, DSc. – member of the Scientific Program Committee of the conference: XLVIII. Bratislavian Oncological Days, Bratislava, 2011

[46] Assoc. Prof. Zajac Vladimír, PhD. – organiser of the conference Probiotics in Oncology), Bratislava, March 7, 2011

iii. List of employees serving in important national scientific bodies (e.g. boards, committees, editorial boards of scientific journals)

[1] Sedlák Ján, DSc. – chairman of Presidium of the Slovak Research and Development Agency

[2] Sedlák Ján, DSc. – member of Medical and Pharmaceutical Sciences Committee of the Grant Agency VEGA

[3] Sedlák Ján, DSc. – member of Scientific Board of the Faculty of Medicine, Comenius University, Bratislava

[4] Sedlák Ján, DSc. – Head of the Chamber of the Assembly of Slovak Academy of Sciences

[5] Sedlák Ján, DSc. – member of Editorial Council of Slovak Academy of Sciences

[6] Sedlák Ján, DSc. – member of Centre of Excellence Program Committee of Slovak Academy of Sciences

[7] Sedlák Ján, DSc. – member of PhD Defense Committee In Oncology

[8] Assoc. Prof. Altaner Čestmír, DSc. – member of DSc. Defence Committee In Genetics

[9] Babušíková Oľga, MD., DSc. – member of DSc. Defence Committee In Genetics

[10] Babušíková Oľga, MD., DSc. – member of DSc. Defence Committee In Antropology

[11] Babušíková Oľga, MD., DSc. – member of DSc. Defence Committee In General Biology

[12] Assoc. Prof. Altaner Čestmír, DSc. – member of DSc. Defence Committee In Oncology

[13] Assoc. Prof. Altaner Čestmír, DSc. – member of DSc. Defence Committee In Virology

[14] Brozmanová Jela, DSc. – member of DSc. Defence Committee In Genetics

[15] Assoc. Prof. Altaner Čestmír, DSc. – member of DSc. Defence Committee In Genetics

[16] Assoc. Prof. Altaner Čestmír, DSc. – member of Scientific College for Molecular Biology and Genetics

[17] Assoc. Prof. Altaner Čestmír, DSc. – member of Scientific Board of Slovak League Against Cancer

[18] Assoc. Prof. Altaner Čestmír, DSc. – member of State Programme and Research & Development Sub-Programme Council “Genomics of cancer, heart and infection diseases for healthier human and animal population”

[19] Ujházy Viliam, MD., DSc. – member of Scientific Board of Slovak League Against Cancer

[20] Babušíková Oľga, MD., DSc. – member of the Scientific Council for Medical Sciences

[21] Luciaková Katarína, DSc. – Scientific Secretary of the Scientific Council for Molecular Biology and Genetics

[22] Chovanec Miroslav, PhD. – member of the Natural Sciences Committee of the Grant Agency VEGA

[23] Poláková Katarína, DSc. – member of the Medical and Pharmaceutical Sciences Committee of the Grant Agency VEGA

[24] Piršel Miroslav, PhD. – deputy of the Natural Sciences Committee of the Grant Agency VEGA

[25] Piršel Miroslav, PhD. – member of PhD Defence Committee In Genetics

[26] Gábelová Alena, PhD. – member of PhD Defense Committee In Genetics

[27] Luciaková Katarína, DSc. – member of PhD Defense Committee In Genetics

[28] Chovanec Miroslav, PhD. – member of PhD Defense Committee In Genetics

[29] Assoc. Prof. Altaner Čestmír, DSc. – member of PhD Defense Committee In Virology

[30] Assoc. Prof. Altaner Čestmír, DSc. – member of PhD Defense Committee In Oncology

[31] Assoc. Prof. Altaner Čestmír, DSc. – member of editorial board of the scientific journal Neoplasma

[32] Ujházy Viliam, MD, DSc. – Chief-Editor of the scientific journal Neoplasma

[33] Sedlák Ján, DSc. – member of editorial board of the scientific journal Neoplasma

[34] Piršel Miroslav, PhD. – member of editorial board of the scientific journal General Physiology and Biophysics

[35] Horváthová Eva, PhD. – member of editorial board of the scientific journal Interdisciplinary Toxicology

[36] Ondrušová Martina, MD., PhD. – member of the editorial board of the scientific journal Urology

iv. List of national awards and distinctions

[1] Assoc. Prof. Altaner Čestmír, DSc. – State Award Rad Ľudovíta Štúra (Ľudovít Štúr Order)

[2] Brozmanová Jela, DSc. – Distinguished Scientist of Slovak Academy of Sciences 2006

[3] Babušíková Oľga, MD., DSc. – Distinguished Scientist of Slovak Academy of Sciences 2010

[4] Kučerová Lucia, PhD. – Young Scientist Award of Slovak Academy of Sciences 2008 (2^{nd} place)

[5] Slameňová Darina, DSc. – Silver Medal, Slovak Medical Society Award 2009

[6] Kučerová Lucia, PhD. – Young Scientist 2008, Journalist Studio Award

[7] Chovanec Miroslav, PhD. – Distinguished Young Scientist of Slovakia 2007, Junior Chamber International Slovakia Award

[8] Jakubíková Jana, PhD. – Distinguished Young Scientist of Slovakia 2007, Junior Chamber International Slovakia Award

[9] Čierniková Soňa, PhD. – Drobnica´s Memorial Award 2007

[10] Čierniká Soňa, PhD. – Young Scientist Award of Slovak Academy of Sciences 2007 (2nd place)

[11] Bohovič Roman, MSc. – Štefan Kužela Award 2008

v. Supplementary information and/or comments documenting international and national status of the Organisation

Several outstanding scientists have visited our Institute and give lectures.

Prof. Jozef Gecz, PhD., Neurogenetics Laboratory, Department of Genetic Medicine, Women`s and Children`s Hospital, Adelaide, Australia

Yongping Bao, PhD., School of Medicine, Health Policy and Practice, University of East Anglia, Norvich NR4 7TJ, United Kingdom

David Basiji, PhD., President and CEO, Amnis Corporation

Dr. Diana Márquez, University of California, USA

Prof. Dr. Wolfgang Mikulits, Laboratory of Epithelial Cell Plasticity, Institute of Cancer Research, Medical University of Vienna, Vienna, Austria

Assoc. Prof. M. Hajdúch, MD, PhD., Pediatrician Laboratory, Children Clinics, LF UP a FN Olomouc, Czech Republic

Assoc. Prof. Erich Heidenreich, Medical University of Vienna, Vienna, Austria

Cancer Research Institute is a unique leading institution with its mission specifically dedicated to the basic and translational molecular oncology research in Slovakia. Our institute further contributes to establish novel methods for molecular-genetic analysis of hereditary forms of several cancer syndromes in Slovakia. The established protocols for the differentiated diagnostic positively influences the clinical management of patients with hereditary predisposition to breast and ovarian cancer, two types of colorectal carcinomas, and medullary thyroid carcinoma. In addition to the detection within the family members the asymptomatic mutation carriers were indentified and enrolled in preventive screening and non-carriers released from psychological stress. The Institute's leading role in the leukemia and lymphoma analysis by flow cytometry in Slovakia is still generally recognized.
The international status is also reflected by the increasing impact factor of the international journal NEOPLASMA recognized as a leading journal in medical sciences in Slovakia.

4. Project structure, research grants and other funding resources

- **International projects and funding**

i. List of major projects within the European Research Area – 6th and 7th Framework Programme of the EU, European Science Foundation, NATO, COST, INTAS, CERN, etc. (here and in items below please specify: type of project, title, grant number, duration, total funding and funding for the Organisation, responsible person in the Organisation and his/her status in the project, e.g. coordinator, work package leader, investigator)

[1] Type of project:	FP6 (COOPERATION)
Title:	**Application-oriented studies on regulatory networks involved in lipid homeostasis and atherosclerosis (Acronym SOUTH)**
Grant number:	FP6-037498 (LSHM-CT-2006-037498)
Duration:	10/2006 – 09/2009
Total funding:	201 954 EUR
Funding of the Organisation:	
Responsible Person in the Organisation:	BARÁTH Peter, PhD.
Status:	Investigator

[2] Type of project:	FP7 (PEOPLE)
Title:	**Identification of Novel Protein Kinases Required for Meiosis**
Grant number:	FP7-PEOPLE-2007-2-1-IEF
Duration:	09/2008 – 08/2011
Total funding:	Personal costs and consumables
Funding of the Organisation:	0 Eur
Responsible Person in the Organisation:	ČIPÁK Ľuboš, PhD
Status:	Investigator

ii. List of other international projects incl. total funding and funding for the Organisation

[1] Type of project:	Multilateral, IARC-funded project
Title:	**Atlas of Cancer Mortality in Europe**
Grant number:	-
Duration:	01/2007 – 12_2009
Total funding:	Personal and travel costs
Funding of the Organisation:	0
Responsible Person in the Organisation:	Assoc. Prof. PLEŠKO Ivan, DSc.
Status:	Investigator

[2] Type of project:	Multylateral, IARC-funded project
Title:	**ACCIS Programme - Automated Chilldhood Cancer Information System**
Grant number:	-
Duration:	01/95 – 12/2009

Total funding: Personal and travel costs
Funding of the Organisation: 0
Responsible Person
in the Organisation: Assoc. Prof. PLEŠKO Ivan, DSc.
Status: Investigator

[3] Type of project: Multilateral, IARC-funded project
Title: **European Cancer Incidence and Mortality Database**
Grant number: -
Duration: 01/88 – 12/2009
Total funding: Personal and travel costs
Funding of the Organisation: 0
Responsible Person
in the Organisation: Assoc. Prof. PLEŠKO Ivan, DSc.
Status: Investigator

[4] Type of project: Multilateral, IARC-funded project
Title: **GLOBOCAN – Cancer Incidence and Mortality Worldwide. IARC Cancer** Database
Grant number: -
Duration: 01/88 – 12/2009
Total funding: Personal and travel costs
Funding of the Organisation: 0
Responsible Person
in the Organisation: Assoc. Prof. PLEŠKO Ivan, DSc.
Status: Investigator

[5] Type of project: Multilateral, IARC-funded project
Title: **European Cancer Health Indicator Project Phase II**
Grant number: -
Duration: 01/2004 – 12/2008
Total funding: Personal and travel costs
Funding of the Organisation: 0
Responsible Person
in the Organisation: Assoc. Prof. PLEŠKO Ivan, DSc.
Status: Investigator

[6] Type of project: Multilateral, IARC-funded project
Title: **European Cancer Incidence**
Grant number: -
Duration: 09/2008 – 08/2011
Total funding: Personal and travel costs
Funding of the Organisation: 0
Responsible Person
in the Organisation: Assoc. Prof. PLEŠKO Ivan, DSc.
Status: Investigator

[7] Type of project: Multilateral, International Visegrad Fund
Title: **5th DNA Repair Workshop**
Grant number: 13074-2007-IVF
Duration: 12/2007 – 12/2008
Total funding: 5000 Eur

Funding of the Organisation:	0
Responsible Person	
In the Organisation:	Piršel Miroslav, PhD.
Status	Co-ordinator of the project

[8]

Type of project:	Bilateral Slovak – Danish project
Title:	**Influence of stem cells on life span of mice**
Grant number:	AU
Duration:	01/2003 – 12/2009
Total funding:	expenses covered by the Danish Organisation
Funding of the Organisation:	0
Responsible Person	
in the Organisation:	ALTANEROVÁ Veronika, PhD.
Status:	Coordinator - Investigator

[9]

Type of project:	Bilateral Slovak – Polish project
Title:	**The role of photoactivation and polyphenols in toxity of mixtures of chemical carcinogens**
Grant number:	17
Duration:	01/2007 – 12/2009
Total funding:	Personal and travel costs
Funding of the Organisation:	0
Responsible Person	
in the Organisation:	GÁBELOVÁ Alena, PhD
Status:	Coordinator - Investigator

[10]

Type of project:	Bilateral Slovak – Taiwan project
Title:	**Arsenic in cancer treatment: mechanism of action and new forms of delivery**
Grant number:	SAS-NSC JRP 2010/03
Duration:	01/11 – 12/2013
Total funding:	75 000 Eur
Funding of the Organisation:	
Responsible Person	
in the Organisation:	SEDLÁK Ján, DSc.
Status:	Coordinator – Investigator

iii. List of other important projects and collaborations without direct funding

[1] Institute of Molecular Cancer Research, University of Zürich, Switzerland (Prof. Josef Jiricny a Dr. Giancarlo Marra)

[2] Research Laboratories, Department of Surgery, Medical University of Vienna, Austria (Dr. Brigitte Wolf)...

[3] Research Group Human Genetics, Division of Medical Genetics UKBB, Center of Biomedicine DKBW, University of Basel, Switzerland (Dr. Karl Heinimann)

[4] Institute of Biomedicine, Pharmacology and Cell Therapy Research Consortium, Helsinki University Central Hospital, Helsinki, Finland (Dr. Esko-m Kankuri)

[5] Carcinogenesis group, Paterson Institute for Cancer Research, Manchester, UK

[6] Lawrence Livermore National Laboratory, BBR Program, Livermore, USA

[7] Cancer Research UK Laboratories, Weatherall Institute of Molecular Medicine, University of Oxford, John Radcliffe Hospital, UK

[8] Department of Pathology, University of Michigan Medical School, 109 Zina Pitcher Place Ann Arbor, USA

[9] University of Salzburg, Department of Cell Biology, Division of Genetics, Research Group: Genetic Toxicology (prof. Petra Eckl)

[10] National Institute of Environmenatl Health Sciences (NIEHS), NIH, Research Triangle Park, NC, USA

[11] Rudolf Virchow Center for Experimental Biomedicine, Institute for Structural Biology, Wuerzburg, Germany

[12] University of Louisville, Depatrment of Pharmacology & Toxicology, Lousiville, Kentucky, USA

[13] New York University, Chemistry Department, New York, USA

[14] Stockholm University, Dept. of Genetics, Microbiology and Toxicology, Sweden

[15] Food and Nutrition/ENRHIM, College of Human Sciences, Texas Tech University, Lubbock, Texas, United States

[16] Developmental Biology/Wenner-Gren Institute, Stockholm University, Stockholm, Sweden

[17] National Centre for Biomolecular Research and Department of Biology, Masaryk University, Brno, Czech Republic

[18] Department of Neurosurgery and Department of Radiation Physics, Lund University Hospital, Lund, Sweden

[19] Department of Genetic and Cellular Toxicology, Stockholm University

[20] Department of Biophysics, Radiation Physics and Ecology and Department of General Physics, Moscow Engineering Physics Institute, Moscow, Russia

[21] Department of Parasitology, Mycology and Water, Swedish Institute for Infectious Disease Control, Solna, Sweden

[22] Department of Biochemistry and Biophysics, Arrhenius Laboratories, University of Stockholm, Stockholm, Sweden

[23] Occupational and Environmental Health, Stockholm County Council, Stockholm, Sweden

[24] Department of Public Health Sciences, and Division of Occupational Medicine, Karolinska Institutet, Stockholm, Sweden

[25] Research Laboratories, Department of Surgery, Medical University of Vienna, Vienna, Austria

[26] Clinical Institute of Medical and Chemical Laboratory Diagnostics, General Hospital of Vienna, Vienna University, Vienna, Austria

[27] Institute of Organic Chemistry, University of Tubingen, Tubingen, Germany

[28] Institute of Inorganic Chemistry, University of Vienna, Vienna, Austria

[29] Department of Human Genetics, University of Utah Health Sciences Center, Salt Lake City, USA

[30] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Kuwait University, Kuwait

[31] School of Medicine, Health Policy and Practice, University of Anglia, NR4 7TJ, Norwich, UK

[32] Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Department of Medical Oncology, Boston, USA

[33] Institute of Biomedicine, Pharmacology, University of Helsinki, Finland

[34] Department of Cell Biology, Faculty of Natural Sciences, University of Salzburg, Salzburg, Austria

[35] Departments of Human Genetics and Oncology, McGill University, Montreal, Quebec, Canada (Dr. Nancy Hamel and Dr. William Foulkes)

[36] Department of Biochemistry and Biophysics, Arrhenius Laboratories, Stockholm University, Stockholm, Sweden

[37] Department of Genome Integrity, Institute of Molecular Genetics, Academy of Sciences of the Czech Republic, Prague, Czech Republic

[38] Department of Genetic Ecotoxicology, Institute of Experimental Medicine, Academy of Sciences of the Czech Republic, Prague, Czech Republic

[39] Department of Chemistry and Toxicology, Veterinary Research Institute, Brno, Czech Republic

[40] Laboratory of Cytokinetics, Institute of Biophysics, Academy of Sciences of the Czech Republic, Brno, Czech Republic

[41] Department of Molecular Endocrinology, Institute of Endocrinology, Prague, Czech Republic Institute of Macromolecular Chemistry of the Academy of Sciences of the Czech Republic, Prague, Czech Republic

[42] ACIU, Medical Faculty of Masaryk University, Brno, Czech Republic

- **National projects and funding[2]**

i. List of State Research Programmes, and their funding

[1] 0

[2]

ii. List of project supported by APVV

[2] Excluding projects for the popularisation of science

Start	Project title	Project number	Duration in months	Funding for theOrganisation (EUR)	Role of the Organisation
2007	Epithelial-mesenchymal transition in the model of breast carcinoma stem cells in vitro	51-017505	03/2006-02/2009	57093.54	Coordinator
	Further in vivo characterisation of the mutant and polymorphic DNA ligase IV proteins found in LIG4 patients	51-042705	05/2006-04/2009	59450.31	Coordinator
	Plant extracts - anti-inflammatory, cytotoxic ans antimutagenic effects in animals	51-015404	01/2005 - 12/2007	6970.72	Partner
	Participation of the central nervous system in monitoring and modulation of tumorigenesis. New approach for the study of cancer etiopathogenesis	APVV-0045-06	01/2007-12/2010	4116.05	Partner

Start	Project title	Project number	Duration in months	Funding for theOrganisation (EUR)	Role of the Organisation
2008	Epithelial-mesenchymal transition in the model of breast carcinoma stem cells in vitro	51-017505	03/2006-02/2009	43616.81	Coordinator
	Further in vivo characterisation of the mutant and polymorphic DNA ligase IV proteins found in LIG4 patients	51-042705	05/2006-04/2009	54238.86	Coordinator
	Human mesenchymal stem cells as cytoreagents for metastasis-targeted therapy	APVV-0260-07	06/2008-12/2011	71931.22	Coordinator
	XPB/XPD DNA helicases: structure-function studies and a role in apoptosis	APVV-0208-07	06/2008-12/2011	33027.95	Coordinator
	Intestinal bacteria in ethiology of colorectal carcinoma and immunodeficiency aquired syndrome	APVV-0404-07	06/2008-12/2011	30505.21	Coordinator
	Participation of the central nervous system in monitoring and modulation of tumorigenesis. New approach for the study of cancer etiopathogenesis	APVV-0045-06	01/2007-12/2010	7857.00	Partner
	Hypericum spp.as a source of bioactive compounds with antitumor activity	APVV-0321-07	02/2008-12/2010	1427.34	Partner
	Centre for Signalosome Research	VVCE-0001-07	07/2008-06/2011	39600.35	Partner

Start	Project title	Project number	Duration in months	Funding for theOrganisation (EUR)	Role of the Organisation
2009	Epithelial-mesenchymal transition in the model of breast carcinoma stem cells in vitro	51-017505	03/2006-02/2009	1128	Coordinator
	Further in vivo characterisation of the mutant and polymorphic DNA ligase IV proteins found in LIG4 patients	51-042705	05/2006-04/2009	11219	Coordinator
	Human mesenchymal stem cells as cytoreagents for metastasis-targeted therapy	APVV-0260-07	06/2008-12/2011	77507	Cooerdinator
	XPB/XPD DNA helicases: structure-function studies and a role in apoptosis	APVV-0208-07	06/2008-12/2011	33359	Coordinator
	Intestinal bacteria in ethiology of colorectal carcinoma and immunodeficiency aquired syndrome	APVV-0404-07	06/2008-12/2011	29675	Coordinator
	Participation of the central nervous system in monitoring and modulation of tumorigenesis. New approach for the study of cancer etiopathogenesis	APVV-0045-06	01/2007-12/2010	5400	Partner
	Hypericum spp.as a source of bioactive compounds with antitumor activity	APVV-0321-07	02/2008-12/2010	1493	Partner
	Centre for Signalosome Research	VVCE-0001-07	07/2008-06/2011	1493	Partner
	Assessment of spontaneous mutagenesis in yeast cells expressing the human DNA ligase proteins found in LIG4 patients	SK-AT-0010-08	02/2009-12/2010	1991	Partner

Start	Project title	Project number	Duration in months	Funding for theOrganisation (EUR)	Role of the Organisation
2010	Human mesenchymal stem cells as cytoreagents for metastasis-targeted therapy	APVV-0260-07	06/2008-12/2011	62404	Coordinator
	XPB/XPD DNA helicases: structure-function studies and a role in apoptosis	APVV-0208-07	06/2008-12/2011	32419	Coordinator
	Intestinal bacteria in ethiology of colorectal carcinoma and immunodeficiency aquired syndrome	APVV-0404-07	06/2008-12/2011	31069	Coordinator
	Participation of the central nervous system in monitoring and modulation of tumorigenesis. New approach for the study of cancer etiopathogenesis	APVV-0045-06	01/2007-12/2010	0	Partner
	Hypericum spp.as a source of bioactive compounds with antitumor activity	APVV-0321-07	02/2008-12/2010	929	Partner
	Centre for Signalosome Research	VVCE-0001-07	07/2008-06/2011	39633	Partner
	Assessment of spontaneous mutagenesis in yeast cells expressing the human DNA ligase proteins found in LIG4 patients	SK-AT-0010-08	02/2009-12/2010	1991	Cooerdinator

Start	Project title	Project number	Duration in months	Funding for theOrganisation (EUR)	Role of the Organisation
2011	Human mesenchymal stem cells as cytoreagents for metastasis-targeted therapy	APVV-0260-07	06/2008-12/2011	0	Coordinator
	XPB/XPD DNA helicases: structure-function studies and a role in apoptosis	APVV-0208-07	06/2008-12/2011	0	Coordinator
	Intestinal bacteria in ethiology of colorectal carcinoma and immunodeficiency aquired syndrome	APVV-0404-07	06/2008-12/2011	0	Coordinator
	DNA repair and preleukemic clones in cord blood stem cells	APVV-0669-10	05/2011-10/2014	94469	Coordinator
	Identification of predictive epigenetic biomarkers in breast cancers	APVV-0076-10	05/2011-10/2014	55534	Coordinator
	Regulation of DNA double-strand repair mechanism choice	APVV-0057-10	05/2011-04/2014	53599	Cooerdinator
	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	10197	Partner
	Hypericin: biotechnology, signalome, photodynamic therapy	APVV-0040-10	05/2011-10/2014	1352	Partner
	Centre for Signalosome Research	VVCE-0001-07	07/2008-06/2011	24522	Partner

iii. Number of 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	2007	2008	2009	2010	2011
number	24	23	22	20	20
funding in the year (EUR)	86,071	94,901	98,745	135,839	147,842

- **Summary of funding from external resources**

External resources	2007	2008	2009	2010	2011	total	average
external resources (milions of EUR)	0.0531	0.0349	0.0326	0.0726	0.0715	0.2647	0.0529
external resources transfered to coooperating research organisations (milions of EUR)	0.0048	0.0489	0.0104	0.0406	0.0360	0.1407	0.0281
ratio between external resources and total salary budget	0.068	0.044	0.039	0.087	0.090	-	0.066
overall expenditures (milions of EUR)	1410	1918	1917	1930	1779	8954.000	1790.800

iv. List of projects the EU Structural Funds

Year	Project title	Project number	Duration in months	Funding for the Organisation (EUR)	Role of the Organisation
2007					
2008					
2009	Center of Excellence for Translational Research in Molecular Medicine	262 401 200 08	05/2009 - 02/2011	0	Partner
2010	Center of Excellence for Translational Research in Molecular Medicine 2	262 401 200 30	01/2010 - 12/2012	0	Partner
	Diagnostics of Socially Important Disorders in Slovakia, based on Modern Biotechnologies	262 402 200 58	11/2010 - 10/2013	0	Partner
	Center of Excellence for Translational Research in Molecular Medicine	262 401 200 08	05/2009 - 02/2011	3090	Partner
	Implementation of radiobiological research of intensity-modulated proton therapy into clinical oncology practice	262 202 201 29	10/2010 - 03/2014	0	Coordinator
2011	Center of Excellence for Translational Research in Molecular Medicine 2	262 401 200 30	01/2010 - 12/2012	9614.9	Partner
	Diagnostics of Socially Important Disorders in Slovakia, based on Modern Biotechnologies	262 402 200 58	11/2010 - 10/2013	2087.06	Partner
	Implementation of radiobiological research of intensity-modulated proton therapy into clinical oncology practice	262 202 201 29	10/2010 - 03/2014	0	Coordinator
	Establishment of the Competence Centre for Research and Development in the Field of Molecular Medicine	26240220071	06/2011 - 09/2014	0	Partner

- **Summary of external resources of the EU Structural Funds (ERDF/ESF)**

CRI SAS is involved in 4 EU SF as a partner and in one project is coordinator.

v. Supplementary info and/or comments on research projects and funding resources

Important external financial sources to support the research projects come from Cancer Research Foundation (CRF). CRF co-finances annually the important new equipment to improve the institutional infrastructure such as Q-PCR with high resolution melting analysis, Nucleofector, Pulse electrophoresis, WAVE system, Elispot. In addition, it supports young scientists by travel grants for participation on international conferences. In addition, Slovak League Against Cancer annually co-financed the Journal Neoplasma, mesenchymal cell research and breast cancer research project. Major funding provided by Scientific Grant Agency of the Slovak Academy of Sciences and the Ministry of Education (VEGA) remains insufficient to reach project goals and therefore the goals have to be achieved with the help of international collaborations (average funding per year per project: ~4000 €). Major problem with the research funding remains in the absence of the functional grant system to open call for proposals regularly to support the scientific research in Slovakia. The Slovak Research and Development Agency did not open general call for proposals for a long-period of time which will certainly be reflected by the major problem in project funding and research continuity.

5. Organisation of PhD studies, other pedagogical activities

i. List of accredited programmes of doctoral studies (as stipulated in the previously effective legislation as well as in the recently amended Act on the Universities). Period of validity of accredited scientific disciplines, characterization of perspectives of PhD study on the Organisation

The Cancer Research Institute is actively involved in the education and training of the undergraduated students (Master thesis) and graduated students (Rigorous Thesis) mainly from the Comenius University (Faculty of Genetics, Medicine and Molecular Biology), and Slovak Technical University. Moreover, the Institute is accredited for doctoral studies based on the recently amended Act on the Comenius University in two PhD. scientific education programs:

[1] Experimental Oncology 7.1.15 (15-14-9) – Medical Faculty, Comenius University

[2] Genetics 4.2.4 (15-03-9) – Faculty of Natural Scineces, Comenius University

[3] ERASMUS programme - cooperation with Department of Microbiology and Virology, Comenius University,

ii. Summary table on doctoral studies (number of internal/external PhD students; number of students who completed their study by a successful thesis defence; number of PhD students who quitted the programme)

PhD study	12/31/2007			12/31/2008			12/31/2009			12/31/2010			12/31/2011		
number of potential PhD supervisors															
PhD students	number	defended thesis	students quitted	number	defended thesis	students quitted	number	defended thesis	students quitted	number	defended thesis	students quitted	number	defended thesis	students quitted
internal	9	5	4	12	2	0	13	5	0	15	2	1	14	0	1
external	1	0	0	1	0	0	1	0	0	1	0	0	0	0	1
supervised at external institution by the research employees of the assessed organisation	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0

iii. Postdoctoral positions supported by

a) ***external funding (specify the source)***

[1] SAIA (Slovenská akademická informačná agentúra - Slovak Academic Information Agency) – Vasilyev Stanislav

[2] ICRETT fellowship – Cavarretta Ilaria

b) ***internal funding - the Slovak Academy of Sciences Supporting Fund of Stefan Schwarz***

[1] Čierniková Soňa, PhD. – 2007

[2] Jakubíková Jana, PhD. – 2007 rok

iv. Summary table on pedagogical activities

Teaching	2007	2008	2009	2010	2011
lectures (hours/year)[3]	41	13	22	15	34
practicum courses (hours/year)[3]	2303	2057	2139	2038	2494
supervised bachelor thesis (in total)	0	0	3	3	3
supervised diploma thesis (in total)	9	21	13	14	12
supervised rigorous thesis (in total)	0	0	0	2	0
members in PhD committees (in total)	4	6	4	6	4
members in DrSc. committees (in total)	1	3	2	1	0
members in university/faculty councils (in total)	0	1	1	1	1
members in habilitation/inauguration committees (in total)	2	2	0	0	1

3

v. List of published university textbooks

[1] ŠTRBÁK, Vladimír - BAČOVÁ, Zuzana - **GÁBELOVÁ, Alena** - HRUBIŠKO, Mikuláš - IMRICH, Richard - VLČEK, Miroslav. Patologická fyziológia. Bratislava: Slovenská zdravotnícka univerzita, 2010. 164 s. ISBN 978-80-89352-40-1...

vi. Number of published academic course books

[1] 0

vii. List of joint research laboratories/facilities with the universities

[1] 0

viii. Supplementary information and/or comments on doctoral studies and pedagogical activities

CRI SAS has signed contract for cooperation with following subjects:

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

- ***Medical Faculty of Comenius University, Bratislava*** in the field of pregraduate and postgraduate program 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 on the joined research groups on particular projects.
    - *Department of Pathological Anatomy and Biology*: 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 conference, diploma and thesis to meet requirements for B.Sc. degree. Assoc prof. V. Zajac gives regularly lectures for the students at the Department of Pathological Anatomy.

- ***Faculty of Natural Sciences, Comenius University, Bratislava,*** in the field of pregraduate and postgraduate program 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 repair of double-strand DNA breaks 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 genotoxocology and is realized in the forms of diploma thesis, publications in research journals and presentations within the scientific conferences.

- ***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 compound 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 from of publications in scientific journals and presentations on international conferences
- ***Slovak Health 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 these bacteria and their specific intracellularization properties. These properties make them real candidates for potential horizontal gene transfer between procaryotic and eucaryotic system.

Based on the long-standing cooperation between CRI SAS and Cancer Research Foundation (CRF), CFR 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.

6. Applied research

(Applications of results)

i. List of the most important results of applied research projects

[1] The **Laboratory of Tumor Immunology** together with hospitals and regional health centers (*National Cancer Institute*, *Department of Pediatric Oncology of the Faculty of Medicine*, *St. Elizabeth's Cancer Hospital*, *Department of Internal Medicine of the hospital Ruzinov*, *Department of Internal Medicine of the hospital of the Ministry of Interior*, *Institute of Haematology and Blood Transfusion*) have realized immunophenotype analyses in bone marrow cells, peripheral blood, lymph nodes in several hundred leukemia children and adults patients using the flow cytometry technique that helps to:

- confirm and specify diagnosis, divide patients into individual prognostic groups of leukemia and lymphomas
- detect early relapses
- monitor the treatment – determination of minimal residual disease (MRD)

[2] In the **Laboratory of Cancer Genetics** and **Laboratory of Molecular Oncology,** the set of determining molecular genetic methods for identification of germline-mutation carriers in patients suffered from hereditary forms of polyposis and non-polyposis colorectal cancer (FAP, Lynch syndrome - HNPCC), breast and ovarian cancer (HBOC) and hereditary thyroid cancer (MEN-2) have been introduced and the results of analyses were used in cancer patient management.

- Until now, we have analyzed 172 families suspected from familial adenomatous polyposis (FAP) from whole Slovakia. Number of families in which was detected germ-line mutation in the *APC* gene is 96. The results were used for therapy, resulted in resection of the main part of colon.
- Molecular diagnostics of hereditary form of breast and ovarian cancer was performed in our laboratory for 132 suspected patients. Mutations in the *BRCA1* and *BRCA2* genes, responsible for predisposition to this form of cancer were found in 43 patients. These results were provided to appropriate clinical departments for consequent therapy.
- We evaluated 104 Lynch syndrome suspected patients and observed DNA mismatch repair deficiency (phenotype of microsatellite instability) in colorectal cancer tissues of 25 patients. In patients selected according to clinical criteria and MSI results we identified 22 original germline mutations in the *MLH1*, *MSH2* or *MSH6* mismatch repair genes using genomic sequencing. Germline mutations of these genes were found in 28 families that are dispensed in preventive health program for Lynch syndrome families to enable an early detection of cancer development.
- Genetic screening of specific population in selected area was performed and confirmed mutation of the RET gene Ala641Ser in two families in the villages Zlatníky a Malé Hoste. The analysis identified the mutation carriers as these might have increased risk of thyroid tumor development and therefore should undertake lifelong preventive monitoring.

[3] In Lynch syndrome patients the epigenetic gene silencing, namely DNA methylation in the *MLH1* mismatch repair gene, was investigated. Our results indicate that MLH1 methylation could serve as an important molecular discriminator between sporadic and hereditary unstable colorectal tumors with dense and weak promoter methylation profiles, respectively. These differences in methylation profiles can lead to more effective molecular diagnosis of Lynch syndrome (Genes Chromosomes Cancer 2008, 47:906-14).

[4] In several Lynch syndrome patients with microsatellite unstable, thereby DNA mismatch repair defected colorectal cancers, we found insertion/deletion mutations in *MRE11* and *RAD50* microsatellite repeats. These patients manifested germline mutations for MRE11/RAD50/NBS1 protein complex destabilization that might increase a risk for additional DSB repair deficiency and acceleration of genome instability (Eur J Hum Genet 2007, 15:922-9).

[5] As the main source of infections during neutropenia is considered endogenous flora. For this purpose we created double-blind, randomized, multicenter, placebo-controlled phase II clinical study aimed at prophylaxis of febrile neutropenia by symbiotic preparation, which is currently underway in pediatric oncology centers in Slovakia. Current results demonstrated not only very good tolerance of administered prophylaxis in pediatric patients, but also its security. To our knowledge this is the first preliminary evidence about safety of the symbiotic therapy in pediatric neutropenic patients.

[6] Polymorphism in the adenomatous polyposis coli (*APC*) gene was analyzed in 33 families suspected of familial adenomatous polyposis (FAP) without identified APC gene mutation. Twelve different types of polymorphism were found in the cohort of the families analyzed. Of the 12 polymorphisms, 11 were silent substitution and only one was responsible for the amino acid change – D1822V, which was identified in 60% of the families analyzed. The most frequently detected polymorphism D1822V is potentially associated with the risk of colorectal cancer. (Neuroendocrinol Letters 2009, 30, Suppl.1: 25-28)

[7] We have participated in a broad international cooperation aimed to estimate the number of generations since the appearance of the mutation c.5266dupC in BRCA1 gene in each population of breast and ovarian cancer patients studied and gain some insight into where and when it arose and how the mutation may have spread throughout Europe to reach its current distribution. Results suggest that BRCA1 mutation c.5266dupC most likely originated in Northern Europe, specifically in Russia or possibly in Denmark, between 1800 and 1500 years ago, from where it had spread by Vikings to the region of Central Europe (European Journal of Human Genetics, 2011, 19: 300-306). This result was selected as the best result of Applied research for Section II – Life, Chemical, Medical, and Environmental Sciences in year 2011.

[8] We have prepared a methodology protocol for National Cancer Institute concerning on the screening of mutations in K-ras gene. The method is based one-base fluorescent extension of specifically desighned primers for selected nucleotides in codons 12 and 13 and the results are achieved by multiplex SNaPshot kit with subsequent detection on genetic analyzer. This protocol should be used in patients treated with inhibitors of EGF receptor, while the presence of mutation makes treatment ineffective.

[9] Relative biological efficiency (RBE) of protons at the Proton Therapy Center in Ružomberok has been validated in the radiotherapeutical dose range using stem cells and lymphocytes from umbilical cord blood (UCB). RBE was 1.01-1.05 in average as measured by fluorescent microscopy and 0.94-0.99 as measured by analysis of DNA repair foci using flow cytometry and fluorescent microscopy. This knowledge is a prerequisite to determine the proton therapeutic doses.

[10] We have studied whether radiofrequency (RF) exposure induce DSB in umbilical cord blood hematopoietic stem cells (HSC) using most sensitive technique to detect DSB that is based on analysis of DSB co-localizing proteins γ-H2AX and 53BP1. In general, RF-exposure did not affect formation of DNA repair foci. However, statistically significant increase in 53BP1 foci was seen following exposure of CD34- cells separated with NH_4Cl at 4 mW/kg. Elucidating the timing and mechanism of DSB repair in HSC may contribute to preventive measures for leukemia and development of new strategies in leukemia cure.

[11] We show that 53BP1 foci are very sensitive endpoint for detection of DSB, biological dosimetry, assessment of individual radiosensitivity and that the post-irradiation time

used for estimation of radiosensitivity at therapeutically relevant doses in proliferating human cells by scoring DNA repair foci should be limited by the duration of the cell cycle (International Journal of Radiation Biology 2007, 83:319-329; International Journal of Radiation Biology 2011, 87:736-745).

[12] We have suggested and tested in experiments new mechanism for formation of residual foci and their persistence based on binding to nuclear matrix and chromatin condensation. Our evaluation of residual foci in human cells *in vitro* and in blood of breast cancer patients undergoing radiotherapy suggests that the residual foci may be useful for biological dosimetry and estimation of individual radiosensitivity in radiotherapy of tumors (Mutation Research 2010, 704:132-141).

[13] We studied whether microwaves (MW) from mobile phones induce DSB or affect DSB repair in stem cells. We found that MW from mobile phones inhibits formation of 53BP1 foci in human lymphocytes, primary fibroblasts and mesenchymal stem cells. Strongest MW effects were always observed in stem cells that suggest both significant misbalance in DSB repair and severe stress response. Our findings that stem cells are most sensitive to MW exposure, do not adapt to chronic exposure, and react to more frequencies than differentiated cells may be important for cancer risk assessment and indicate that stem cells are most relevant cellular model for validating the safe mobile communication signals (Bioelectromagnetics 2009, 30:129-141; Environmental Health Perspectives 2010, 118:394-399).

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

[1] Assoc. Prof. Pleško Ivan, MD., DSc. – cooperation with the establishment of National Cancer Register in Slovakia

[2] Ondrušová Martina, PhD. – cooperation with the establishment of National Cancer Register in Slovakia

[3] Assoc. Prof. Pleško Ivan, MD., DSc. – cooperation with the edition of year-books „Incidencia zhubných nádorov v Slovenskej republike“ (Cancer Incidence in Slovakia)

[4] Ondrušová Martina, PhD. – cooperation with the edition of year-books „Incidencia zhubných nádorov v Slovenskej republike“ (Cancer Incidence in Slovakia)

[5] Assoc. Prof. Pleško Ivan, MD., DSc. – Provision of cancer incidence data to League Against Cancer

[6] Bartošová Zdena, PhD. – member of Government Council for non-governmental and non-profit organizations, representative of Cancer Research Foundation

[7] Gábelová Alena, PhD. –cooperation with the National Contact Point for Scientific and Technical cooperation with the European Food Safety Authority (EFSA) in Slovakia, expert in nanotoxicology

CRI SAS *via* the outcomes of National Oncology Registry indirectly mediates the formulation of guidelines for the decision sphere to undertake measures in the population health. Recent decision of the Ministry of Health has transferred the National Cancer Register to become integral part of the National Centre for Health Information (NCHI). Therefore these activities are provided now by NCHI.

iii. List of licences sold abroad, incl. revenues

[1] 0

iv. List of licences sold in Slovakia, incl. revenues

[1] 0

v. List of contracts with industrial partners, incl. revenues[4]

Project funded by the Non-Profit Organizations

[1] **League against Cancer Foundation**

- Targeted gene therapy of human tumors by means of mesenchymal stem cells isolated from adipose tissue
- Interaction of human mesenchymal stem cells deived from adipose tissue with human tumor cells
- Isolation of human mesenchymal stem cells and their use in regenerative and gene therapy
- MLH1 promoter hypermethylation in relation to the defect of mismatch repair in colorectal cancers
- Nanoparticles in cancer gene therapy and labeling of human stem cells with magnetic fluid and their follow up by MRI
- New epigenetic markers for aggressive forms of breast cancer
- Modification of biological properties in mammary malignant cells

[2] **SPP Foundation (Slovak Gas Industry Foundation)**

- Stem cell-based gene therapy for cancer

[3] **SAIA (Slovak Academic Information Agency)**

- Residual foci assay for prediction of radiosensitivity of breast cancer patients

[4] **Cancer Research Foundation**

- Implementation of histology and molecular-biology methods in the tumor heterogenity analysis

[5] **Jan Korec Foundation**

- Genetic analysis of inhabitants coming from Zlatniky and Male Hoste

Collaboration with Hospitals and Clinical Institutions

[1] Department of Gastroenterology, Department of Internal Medicine, National Cancer Hospital (NCI), Bratislava, Slovak Republic

[2] Department of Mammology and Department of Pathology, St. Elizabeth Cancer Institute, Bratislava, Slovak Republic

[3] Department of Clinical Genetics, St.Elizabeth Cancer Institute, Bratislava, Slovak Republic

[4] University Children's Hospital, Banska Bystrica, Slovak Republic

[5] Department of Pathology and Department of Molecular Biology, Jessenius Faculty of Medicine, Comenius University and Faculty Hospital, Martin, Slovak Republic

[6] Department of Children Oncology, Slovak Medical University, Bratislava, Slovak Republic

[7] The National Institute of Cardiovascular Diseases, Bratislava, Slovak Republic

[8] National Institute of Endocrinology and Diabetogy, Ľubochňa, Slovak Republic

Collaborations with Commercial Companies

[1] S&D Pharma SK s.r.o., Bratislava, Slovak Republic

[2] Cytopathos Ltd., Bratislava,, Slovak Republic

vi. List of research projects with industrial partners, incl. revenues[4]

[1] PLEURAN s.r.o., Bratislava – a biotechnology company engaged in the development, production, and marketing of high quality, natural immuno-modulating products for the support of good health.
Subject: analysis of clinical samples,
Reimbursement: 4 500 Eur

[2] Eurocord–Slovakia, Slovenský register placentárnych krvotvorných buniek (Slovak Register of placental haemopoetic cells)
Subject: analysis of immunological parameters of umbilical cells
Reimbursement: 1 435 Eur

[3] Fidura Capital Consult GmbH., Germany
Subject: The use of human mesenchymal stem cells isolated from adipose tissue in targetted cancer gene therapy
Reimbursement: 18 000 Eur

[4] Keramit
Subject: Validation of Keramit ability to modify stress/genotoxic effects induced in human cells by electromagnetic fields/ionizing radiation
Reimbursement: 3 000 Eur

[5] Daiwa Pharmaceutical Ltd. company, Japan
Subject: Monitoring of immunological parameters of multiple myeloma patients during course of Biobran consumption
Reimbursement: 90 000 US dollars

[6] Environmental Health Trust
Subject: In vitro research on RF-EMF induced DNA alterations in three cell types
Reimbursement: 13 700 €

[7] INFREDpharm, s.r.o.
Subject: measurement of cytotoxicity, cell cycle a apoptosis in the model of human leukemic cell lines
Reimbursement: 3 820 €

[8] University of Oslo, Oslo, Nórsko
Subject: subcontract of 7RP EU HEALTH-F2-2009-222741 (METOXIA)
Reimbursement: 10 000 Eur

[4] If not included in documentation of projects in chapter 4 (Projects structure, research grants and other funding resources).

vii. Supplementary information and/or comments on applied activities

	2007	2008	2009	2010	2011	total
studies for the decision sphere, government and NGOs, international and foreign organisations						0

Participation in draft preparation of National oncological programme, Ministry of Health, 2010-2011

Review about research activities performed in Slovakia in oncological prevention for Ministry of Health 2010

7. Popularisation of Science (outreach activities)

i. List of the most important popularisation activities

[1] Organisation of “Open House“ at the Cancer Research Institute

[2] Presentation results at public exhibitions (INCHEBA, Slovenskí vzdelanci (Slovak Intellectuals) - Doctissimi Slovaciae; EUROBIOTECH)

[3] Organization the press conferences

[4] Publishing articles in press media and internet

[5] Appearances in telecommunication media

[6] Preparing public popularisation lectures

[7] Participation at the fund-raising campaigns organized by Cancer Research Foundation (Run for Life, Fighting Cancer on Wheels)

[8] Co-organization with CRF the project “Scientific Workshop Oncology”

[9] Co-organization with CRF the Young Oncologists Competition

[10] Co-organization with CRF several scientific undertakings at the Cancer Research Day (March 7)

ii. Summary of outreach activities

Outreach activities	2007	2008	2009	2010	2011	total
articles in press media/internet popularising results of science, in particular those achieved by the Organization	60	4	6	10	3	83
appearances in telecommunication media popularising results of science, in particular those achieved by the Organization	25	8	4	12	7	56
press conference	2	1	2	2	0	7
public popularisation lectures	7	8	1	2	89	107

Scientists from the CRI SAS very actively contribute to organization and regularly participate on activities organized by Cancer Research Foundation. The aim is both to raise funds from public donations and supporters and also to increase the public information on the modern trends in cancer research and problems faced in the cancer research. Scientists have prepared information for the press releases to help the public understanding the recent developments and activities. They actively recruit young scientists and encourage them to take part in the competition organized biannually to recognize the best student presentations. The Institute staf has contributed to the decision process by scientific advice as well. Some students recruited were even from secondary school with the aim to further go on with the research career. Researchers have prepared practical demonstrations for the student of secondary schools and public within the research facility to demonstrate some basic research techniques, they increased the knowledge and contributed to the cancer prevention by series of lectures performed during the Oncology Workshop project, they have contributed to the organizational part during the Run for life project, they participated on many of them with their families and friend in order to support the project and increase its public recognition.

iii. Supplementary information and/or comments on popularisation activities

Scientists from the CRI SAS regularly participate on the exhibitions.

- Exhibition INCHEBA EXPO BRATISLAVA organized on May 17–19, 2007. Some results achieved within the project Genomics of the cancer disease for the better population health were presented. The exhibition entitled Methodological Letters for the human genome analysis workflow represented results from four institutes including CRI SAS and it was awarded the Golden Medal of INCHEBA. The researchers presented the outcomes of the preject within the three panels:
    - Leukenie immunophenotyping – improves the leukemia diagnosis and patient treatment – with the direct impact for the cancer patient)
    - Exploitation of the stem cell in the cancer treatment – Troyan horse in oncology – with the direct impact for the cancer patient)
    - Hereditary predisposition to cancer – biological timebomb (From the results of the state programme of research and development executed in CRI SAS with the direct impact for the cancer patient)

- Exhibition: 6th exhibition Slovenskí vzdelanci - Doctissimi Slovaciae
  Place: Bratislava, Slovensko (Exhibition Hall of Ludovit Stur in University Library)
  Lifetime achievements of Branko Chorváth, MD., PhD., scientist from the CRI.

- Exhibition: Central European Congress of Life Sciences EUROBIOTECH 2008
  Place Krakow, Poland.
  Members of the Molecular Oncology Laboratory took part on the exhibition and the poster presented won firts place for the best poster presentation on EUROBIOTECH 2008.

- Exhibition: INCHEBA EXPO Bratislava, 2009
  Outcomes: Presentation of the activities of the project Centre of Excellence CeXignal

- In 2011, CRI SAS celebrated its 65th anniversary, this occation was commemorated by a conference at which former directors, successful alumni and Ph.D. students presented their speeches.

8. Background and management. Staffing policy and implementation of recommendations from previous assessments

i. Summary table of personnel

Personnel	2007	2008	2009	2010	2011
all personnel	128	127	137	111	101
research employees from Tab. Research staff	74	74	73	67	61
FTE from Tab. Research staff	54.9	58.6	58.0	50.7	41.5
average age of research employees with university degree	45	47.2	46.8	46.9	47.9

ii. Professional qualification structure (as of 31.12. 2011)

FEMALE	AGE								
Number of	< 30	31 - 34	35 - 39	40 - 44	45 - 49	50 - 54	55 - 59	60 - 64	> 65
DrSc. / prof. [5]							1		3
II.a / Assoc. prof. [6]		3	1	2		1			2
other researchers PhD./CSc.	2	4	6	2			2	1	
doc./Assoc. prof.									

5 6
,

[5] Responsibility to organize PhD study
[6] Responsibility to be a supervisor of PhD study

iii. Professional qualification structure (as of 31.12. 2011)

MALE	AGE								
Number of	< 30	31 - 34	35 - 39	40 - 44	45 - 49	50 - 54	55 - 59	60 - 64	> 65
DrSc. / prof. [5]						2	2		2
II.a / Assoc. prof. [6]		1	3	1		3			2
other researchers PhD./CSc.	1		3	1				4	
doc./Assoc. prof.						1			2

iv. Status and development of research infrastructure incl. experimental, computing and technical base (description of the present infrastructure, premises, and material and technical resources. Infrastructure, instrumentation and major technical equipment necessary for the achievement of the objectives specified in the research Concept)

Major equipments at the institute include:

- System PALM MicroBeam Laser Capture Micro-dissection (LCMD) allows the isolation of single cells or populations of cells from tissue – histological sections, blood smears, cytologic preparations or tissue cultures.
- Beckman Coulter Epics Altra Flow Cytometer features the capability to analyze and sort on up to 6 colors simultaneously while performing complex multi-parameter applications.
- ABI PRISM 310 Genetic Analyzer is an automated single-capillary genetic analyzer designed for a wide range of sequencing and fragment analysis applications.
- Fluorimeter PolarStar Optima and LUMIstar enables to detect signal in 96-well format and multiplex proliferation, cytotoxicity, fluorescent reporter and viability data
- Wave DHPLC System uses denaturing high performance liquid chromatography (DHPLC) and may be used in applications for detecting genetic variation and fragment sizing.
- Real-Time Cycler PCR Cycler CFX96 allows not only molecular diagnostics, gene expression analysis, highly sensitive detection and quantification, but also analysis of copy number, validation of microarray, detection of sequence and methylation variation and fluorescence detection.
- CHEF-DR III System Pulse-Field Gel Electrophoresis is an advanced pulsed—field system based on the CHEF (clamped homogeneous electric fields) technique.

- Automatic Scanning Analysing System (Metafer). Fluorescence microscope equipped with a versatile high-throughput slide scanning platform Metafer automates a wide area of microscopic image analysis applications for life sciences.

- PyroMark Q24 allows the exact quantitative methylation data of each CpG dinucleotide in analyzed promoter sequence.

- Image Stream equipped with 3 lasers represents the combination of microscope and flow cytometer i.e. it overcomes the flow cytometry disadvantage - the absence of topographic fluorescence distribution analysis

- Elispot quantifies the amount of soluble cytokines/chemokines produced from activated cells, mainly in the field of immunology

The Institute has facilities for work with mutagens, GMO and radioactivity and possess modern animal house which is equipped with two semi rigid isolators for maintenance of athymic Balb/c nu/nu and SCID/beige mice. In addition, the Institute has intranet information system Forum and grant information system G.I.S.

v. Describe how the results and suggestions of the previous assessment were taken into account

CRI SAS has signed an agreement with the Polish Institute of Agricultural Medicine in Lublin. This collaboration is focused on the molecular and cellular biology, genetics and immunology to study the basic mechanisms of neoplastic transformation, prevention of cancer, on the effects of exogeneus and endogeneus factors, including the environmental factors, on carcinogenesis.
The scientists from CRI SAS have participated in a broad interantional study aimed to estimate the number of generations since the appearance of the mutation c.5266dupC in BRCA1 gene in each population of breast and ovarian cancer patients. There were 3 outstanding scientists in the field of Cancer Genetics from collaborating Department of Genetics and Pathomorphology, International Hereditary Cancer Center, Pomeranian Medical University, Szczecin, Poland – Prof. Jan Lubinsky, Dr.Jacek Gronwald, Dr. Bohdan Gorski.

Grant Application and Research Exchange Support office has been created.

Organization of the Institute has been changed into larger Laboratories with similar research interests. There has also been an intensified collaboration between investigators and research programmes (a common project of the Laboratory of Molecular Genetics and the Laboratory of Molecular Biology, APVV, principal investigator Miroslav Chovanec). More recently, the Laboratory of Molecular Biology has merged with the Laboratory of Mutagenesis and Carcinogenesis and research of the new Laboratory is now focused on molecular mechanism(s) of biological effects of nanoparticles (principal investigator Alena Gabelova).

New methodology and technology: ImageStream, Elispot, Metafer image analysis

vi. Supplementary information and/or comments on management, research infrastructure, and trends in personnel development

CRI SAS has a collaboration based on signed contracts with following institutions:

- Molecular Medicine Centre SAS (Bratislava) in the field of development and providing high quality molecular diagnostics by integrating up-to-date technologies of molecular medicine and scientific expertise in national and international academic context.

- St. Elizabeth Cancer Institute (Bratislava) in the field of interconnection of basic and applied cancer research with the aim to efficiently transfer the research knowledge to the clinical practice. It is also focused on increase in the training and practical experience specifically in the area of oncology, immunology and laboratory techniques with their direct participation in the training activities.
- National Cancer Institute (Bratislava) in the field of joint exploration of infrastructure, human resources and space with the aim of functional interconnection of basic and applied research in oncology and genetics. The cooperation should increase the practical experience and improve the knowledge of researchers in both institutions by mean of education in the field of oncology and genetics with their direct participation in educational activities.

Infrastructure: The Institute's location in the old building reflects the urgent need for the reconstruction. Its inner organization does not comply with the up-to-date requirements according to the guidelines for the work with genetically modified organisms, good laboratory practise, biological factors and least but not least the very expensive laboratory devices require air-conditioning for the proper function. No systemic measures due to the lack of finance could have been undertaken to solve the problem with the animal facility to comply with the requirements from the legal authority which further complicates the animal handling and experiments specifically with the vulnerable immunodeficient mouse strains.

Other information relevant to the assessment

Cancer disease is faced by every third citizen of Slovakia, as well as citizen of the European during his/her life. Therefore it should become one of the priorities within the society to support the cancer research and undertake all the preventive and curative measures to decrease this high prevalence and reduce the socio-economical consequences for both the patients and their relatives. On one side the scientific community should be willing to cooperate with the decision sphere to guide the research efficiently and support the effort toward the public knowledge on the potential efficient cancer prevention. On the other side all this efforts are not systemically supported by the authorities, although the EU structural funds money represents the unrepeatable opportunity to improve reseach infrastructure, but the support of personal infrastructure lack of systemic national grant support. Unless the situation changes and the priority is not given to the public health improvement, the research as such will not be able to further keep up with the up-to-date concepts of modern oncology medicine to be 4P: predictive, preventive, personalized and participatory.

ERRATA

2007 year

Mistake: the article is listed as nonCC article in Annual Report 2007 (AR2007).

- Ondrušová, M. - Ondruš, D.: Epidemiology and treatment delay in testicular cancer patients: a retrospective study. In **International Urology and Nephrology**. Vol. 38 no. (2007), p. 1-6

Correction:
Article should be issued in 2008 as CC article.

- Ondrušová, M. - Ondruš, D.: Epidemiology and treatment delay in testicular cancer patients: a retrospective study. In **International Urology and Nephrology**. Vol. 40 no. 1 (2008), p. 143-148. (0.912-IF2008)

2008 year

Mistake: these two articles appeared incorrectly in AR2008 as CC articles despite the affiliation is missing.

- Gregan J, Rumpf C, Li Z, Čipák Ľ: What makes centromeric cohesion resistent to separase cleavage during meiosis I but not during meiosis II?-2008-CELL-CYCLE-VOL7-P151. IF: 4.120

- Čipák Ľ, Spirek M, Gregan J: Sister chromatids caught in the cohesin trap-2008-NATURE-STRUCTURAL-AND-MOLECULAR-BIOLOGY-VOL15-P899. IF: 10.987

Correction:
Both articles are deleted from the list of CC articles 2008 in accreditation Annex 1 file.

Mistake: these three articles are listed as CC article in AR2008, but all were issued in 2009

- Belyaev, I. - Marková, E. - Hillert, L. - Malmgren, L. - Persson, B.: Microwaves From UMTS/GSMMobile Phones Induce Long-Lasting Inhibition of 53BP1/-H2AX DNA Repair Foci in Human Lymphocytes. In **Bioelectromagnetics**. 2008

- Patila, T. - Ikonen, T. - Kankuri, E. - Uutela, A. - Lommi, J. - Krogerus, L. - Salmenpera, P. - Bizik, J. - Lauerma, K. - Harjula, A.: Improved diastolic function after myoblast transplantation in a model of ischemia-infarction. In **Scandinavian Cardiovascular Journal**. 2008

- Repický, A. - Jantová, S. - Čipák, Ľ.: Apoptosis induced by 2-acetyl-3-(6-metoxybenzotiazo)-2-ylamino-acrylonitril in human leukemia cells involves ROS-mitochondrial mediated death signaling and activation of p38 MAPK. In **Cancer Letters**. 2008

Correction:
Articles are listed as CC article of 2009 year in accreditation Annex 1 file.

- Belyaev, I. - Marková, E. - Hillert, L. - Malmgren, L. - Persson, B.: Microwaves From UMTS/GSMMobile Phones Induce Long-Lasting Inhibition of 53BP1/-H2AX DNA Repair Foci in Human Lymphocytes. In **Bioelectromagnetics**. Vol. 30 no. 10.1002/bem.20445 (2009), p. 129-141. (2.759-IF2009)

- Patila, T. - Ikonen, T. - Kankuri, E. - Uutela, A. - Lommi, J. - Krogerus, L. - Salmenpera, P. - Bizik, J. - Lauerma, K. - Harjula, A.: Improved diastolic function after

myoblast transplantation in a model of ischemia-infarction. In **Scandinavian Cardiovascular Journal**. Vol. 43 no. (2009), p. 100-109. (1.07-IF2009)

- Repický, A. - Jantová, S. - Čipák, Ľ.: Apoptosis induced by 2-acetyl-3-(6-metoxybenzotiazo)-2-ylamino-acrylonitril in human leukemia cells involves ROS-mitochondrial mediated death signaling and activation of p38 MAPK. In **Cancer Letters**. Vol. 277 no. 1 (2009), p. 55-63. (3.741-IF2009)

Mistake: the article is listed as nonCC article in AR2008

- JANTOVÁ, S. - REPICKÝ, A. - LETAŠIOVÁ, S. - ČIPÁK, Ľ.: 4-Amino-3-acetylquinoline-induced apoptosis of murine L1210 leukemia cells involves ROS-mitochondrial mediated death signaling and activation of p38 MAPK. In Cell Biochemistry and Function. Vol. 26 no. 5 (2008), p. 609-619.

Correction:
Article is placed in 2008 list as CC article (1.333-IF2008) in accreditation Annex 1 file.

Mistake: these two articles are not listed in AR2008

- PIRNIK, Z. - BUNDZIKOVA, J. - BIZIK, J. - HULIN, I. - KISS, A. - MRAVEC, B.: Activity of brain stem groups of catecholaminergic cells in tumor-bearing rats: response to immobilization stress.. In Annals of the New York Academy of Sciences. Vol. 1148 no. (2008), p. 141-147. (2.303-IF2008)

- Lakota, J. - Škultety, L. - Dubrovčáková, M. - Altaner, Č.: Presence of serum carbonic anhydrase autoantibodies in patients relapsed after autologous stem cell transplantation indicates an improved prognosis. In **Neoplasma**. Vol. 55 no. 6 (2008), p. 486-490. (1.179-IF2008)

Correction:
Articles are listed among CC articles 2008 in accreditation Annex 1 file.

2009 year

Mistake: these two articles were placed in nonCC list of articles in AR2009

- VALASKOVA, Z. - LACKOVICOVA, L. - VRABCOVA, M. - BIZIK, J. - PERZELOVA, A. - MACIKOVA, I. - DANIHEL, L. - KINOVA, S. - BUCKINGHAM, T. - HULIN, I.: Does incorporation of gene for green fluorescent protein in BP6 fibrosarcoma tumor cells depress their intraperitoneal growth in rats?. In Bratislavské lekárske listy. Vol. 110 no. 3 (2009), p. 127-132. (0.317-IF2009)

- LOW, D. - ANG, Z. - YUAN, Q. - FRECER, V. - HO, B. - CHEN, J. - DING, J.: A novel human tectonin protein with multivalent beta-propeller folds interacts with ficolin and binds bacterial LPS.. In PLoS One. Vol. 4 no. 7 (2009), p. 6260-6264. (4.351-IF2009)

Correction:
Both articles are placed in the 2009 CC list in accreditation Annex 1 file.

Mistake: the article was not listed in AR2009

- WACHSMANNOVÁ, L. - ŠTEVURKOVÁ, V. - ADAMČÍKOVÁ, Z. - HOLEC, V. - ZAJAC, V.: Polymorphisms in the adenomatous polyposis coli gene in Slovak families suspected of FAP. In Neuroendocrinology Letters. Vol. 30 no. 1 (2009), p. 25-28. (1.047-IF2009)

Correction:
The article is placed in the 2009 CC list in accreditation Annex 1 file.

Mistake: the article appeared incorrectly in AR2009 as CC articles despite the affiliation is missing.

- Čipák Ľ, Spirek M, Novatchkova M, Chen Z, Rumpf C, Lugmayr W, Mechtler K, Ammerer G, Csaszar E, Gregan J: An improved strategy for tandem affinity purification-tagging of Schizosaccharomyces pombe genes-2009-PROTEOMICS-VOL9-P4825. IF: 4.426

Correction:
The article is deleted from the list of CC articles 2009 in accreditation Annex 1 file.

2010 year

Mistake: the article was listed as nonCC one in AR2010

- PEURA, M. - SILTANEN, A. - SAARINEN, I. - SOOTS, A. - BIZIK, J. - VUOLA, J. - HARJULA, A. - KANKURI, E.: Paracrine factors from fibroblasts aggregates in a fibrin-matrix carrier enhances keratinocyte viability and migration. In Journal of Biomedical Materials Research Part A. Vol. 95 no. 2 (2010), p. 658-664.

Correction:
Article is placed in 2010 list as CC article (3.044-IF2010) in accreditation Annex 1 file.

2011 year

Mistake: this article is listed in AR2011, but was issued in 2012

- PEURA, M. - KAARTINEN, I. - SUOMELA, S. - HUKKANEN, M. - BIZIK, J. - HARJULA, A. - KANKURI, E. - VUOLA, J.: Improved skin wound epithelization by topical delivery of soluble factors from fibroblasts aggregates. In Burns. Vol. 37 no. (2011), p. 1-10. (1.718-IF2011)

Correction:
The article is not listed among CC 2011 list in accreditation Annex 1 file.

Mistake: the article was not listed in AR2011

- EGYUDOVÁ , K. - SILTANEN, A. - KANKURI, E. - BIZIK, J.: Leukemic cells modulate induction of COX-2 in human stromal fibroblasts. In Neoplasma. Vol. 58 no. 6 (2011), p. 525-531. (1.449-IF2011)

Correction:
The article is placed in the CC 2011 list in accreditation Annex 1 file.