Questionnaire

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

Period: January 1, 2003 - December 31, 2006

I. Formal information on the assessed Organisation:

1. Legal name and address

Cancer Research Institute of Slovak Academy of Sciences
Vlarska 7
83391 Bratislava
Slovak Republic

2. Executive body of the Organisation and its composition

Directoriat	name	age	years in the position
director	Assoc.Prof. Čestmír Altaner, PhD., DSc.	73	1995-
deputy director	Sedlák Ján, PhD.	49	2003-
scientific secretary	Zdena Bartošová, PhD.	43	2005-

3. Head of the Scientific Board

Katarína Luciaková, PhD., DSc.

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 2003, 2004, 2005, 2006 and average number during the assessment period

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

Research staff	2003		2004		2005		2006		average	
	No.	FTE	No.	FTE	No.	FTE	No.	FTE	No.	FTE
organisation in whole	48	37.5	50	37.5	50	37	59	46.25	51.75	39.563
Laboratory of Molecular Oncology	0	0	10	6	12	5.75	13	7.75	8.75	4.875
Laboratory of Tumor Immunology	3	3	9	8	10	8.5	12	10.5	8.5	7.5
Laboratory of Cancer Genetics	5	3	8	5	7	5	9	8	7.25	5.25
Laboratory of Molecular Biology	5	2.25	5	3.25	4	3	6	5	5	3.375
Laboratory of Mutagenesis and Carcinogenesis	6	5	9	7	8	6.75	9	6.75	8	6.375
Laboratory of Molecular Genetics	7	7	7	7	7	6.75	7	6.75	7	6.875
Cancer Epidemiology Group	1	0.5	1	0.5	1	0.5	2	0.75	1.25	0.5625
Neoplasma, Chief-Editor	1	0.75	1	0.75	1	0.75	1	0.75	1	0.75
Laboratory of Molecular Virology	7	4	0	0	0	0	0	0	1.75	1
Laboratory of Molecular Immunology	5	5	0	0	0	0	0	0	1.25	1.25
Laboratory of Experimental Therapy	6	5	0	0	0	0	0	0	1.5	1.25
Laboratory of Tumor Cell Biology	2	2	0	0	0	0	0	0	0.5	0.5

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 2003, 2004, 2005, 2006, and average amount for the assessment period

Salary budget	2003	2004	2005	2006	average
total salary budget (millions of SKK)	19.614	19.985	20.942	21.814	20.589

[1] Sum of the brutto salaries without the fund contributions.

6. URL of the Organisation's web site

http://www.exon.sav.sk

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

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

Cancer Research Institute SAS is devoted to molecularly-oriented basic and translational research. Its scientific activity has been focused mainly to:

- DNA damage and repair
- mechanisms of oncogenes and tumor suppressor genes function
- tumor cell biology both normal and cancer stem cells, metastasis
- pathways governing cell growth and types of cell death
- cellular signaling pathway effects of natural and synthetic compounds
- retrovirus vectors for cancer gene therapy
- detection of mutagenic and carcinogenic potential of chemicals on cellular, chromosomal and DNA level
- testing of new anti-cancer drugs and mechanism of their action
- detection and molecular basis of cancer hereditary predisposition
- leukemia and lymphoma immunophenotyping
- descriptive and analytical cancer epidemiology with output to government and decision sphere

The Institute is approved for teaching Ph.D. students in Oncology and Genetics.
It has been the editor of the international CC journal NEOPLASMA for 54 years

2. Summary of R&D activity pursued by the Organisation

Summary of Research and Development activity pursued in the Cancer Research Institute of SAS through 2003 - 2006

Cancer Epidemiology Group

The Laboratory has been invited to participate on several international epidemiological projects of the EU. In the frame of EUROCARE -3 project for the first time the rates of survival of cancer patients (by individual cancer sites and gender) diagnosed in period 1978-1994 in Slovakia could be adequately compared with corresponding rates obtained in selected countries of Europe. Only the data from Slovenia, Estonia and Slovakia covered the whole countries in Eastern Europe and were largely used for comparisons *(Ann.Oncol. 2003, Suppl.5p.41-60; Int. J.*

Cancer 112,2004, 1056-1064, and 109, 2004,598-610, and two monographs of IARC). In the frame of "high resolution study" the detailed data using subsites, clinical stage and morphologic type of tumors were compared for selected major cancer sites (Eur.J.Cancer in press), while in ACCIS study the similar comparisons were performed for childhood cancers *(Eur. J.Cancer 2006, 42, 2150-2169).* Data from Slovakia were largely used and cited abroad because of their accuracy and reliability as well as for respecting the details and could be used also for improving the results of treatment in this country*. (J. Clin. Oncol. 23, 2005, 3742-51, Crit.Rev. Oncol.Haematol. 54,2005, 117-128)*

Laboratory of Mutagenesis and Carcinogenesis

The research activity has been devoted to the molecular and cellular mechanisms of chemical carcinogenesis with emphasis on the tissue specificity of chemical carcinogens. 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. Obtained results were published in peer-reviewed journals, which provides evidence of the relevance of this investigation from the international aspect (*Toxicol. In Vitro. 2003; 17: 457-63*; *Environ. Mol. Mutagen. 2004; 44 (5): 448-58*; *Neoplasma. 2004; 51 (6): 443-50*; *Chem. Biol. Interact. 2004; 148 (3): 163-71*; *Mutagenesis. 2004; 19: 269-76; Mutat. Res. 2004; 560 (2): 91-9; Neoplasma. 2005; 52 (6): 450-5; Mutat. Res. 2006; 593: 43-56; Mutat. Res*. *2006; 593 (1-2): 97-107; Neoplasma. 2006; 53 (6): 485-91; Toxicol. Lett*. *2006; 164 (1): 54-62*). As a member of the EU-funded project (R&D project of the 5th FP), the research staff contributed to the risk assessment of complex organic mixture associated the respirable airborne particles. 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. Besides the mechanisms underlying the adverse biological effects of air pollution, the research was aimed at the interactions of individual components in a mixture that might substantially modulate (enhance/reduce) the biologic activity of the mixture (*Mutat. Res. 2003; 544: 397-402; Mutat. Res. 2004; 563: 49-59; Mutat. Res. 2004; 557: 167-175*; *Environmental Health in Central and Eastern Europe, Donnelly, K.C.; Cizmas, Leslie H. (Eds.),* 2006, XXII, 249 p., *Springer Netherlands; Mutat. Res. Special Issue, two papers - in press*). The exploration in the field of experimental therapy was pointed at computer-assisted combinatorial chemistry methods which allowed design of new promising therapeutic drugs. Importance of such research confirms a close collaboration with outstanding European laboratories and publication of the results in prestigious journals (*J. Mol. Graph. Model. 2003; 22 (3): 209-20; Antimicrob. Agents. Chemother. 2004; 48: 3349-57; Internet Electron. J. Mol. Desn. 2004; 3: 295-307; Combinatorial Chemistry and Technology*, *S. Miertus, G. Fassina, (eds.), 2nd ed., M. Dekker, New York 2004, Chapter 4, 55-74; Bioorg. Med. Chem. 2005; 13: 5492-501; Lett. Drug. Des. Discov. 2005; 2: 638-46*). In agreement with the worldwide current trends, an extensive research activity has been devoted to molecular and cellular mechanisms underlying the chemoprotective potential of vitamins and natural substances with emphasis on the antioxidant capacity since the accumulation of oxidative damage in DNA is implicated in various degenerative processes including carcinogenesis and aging. The free radical scavenging capacity of natural substances isolated from plants, fruit or vegetable was investigated both *in vitro* and *ex vivo* (*Basic Clin. Pharmacol. Toxicol. 2004; 94: 282-90; Neoplasma. 2004; 51(5): 327-33; Neoplasma. 2004; 51 (5): 395-9; Neoplasma. 2004; 51 (6): 407-14; Mutat. Res. 2005; 565: 105-12; Neoplasma. 2005; 52 (6): 450-5; Neoplasma. 2006; 53 (4): 337-42; Oncol. Rep. 2006; 16 (3): 617-24; Mutat. Res. 2006; 600 (1-2): 131-7; Neuro. Endocrinol. Lett*. *2006; Suppl. 2: 44-7*). In addition, the research interests were stressed on substances isolated from the fungal cell wall (glucans) and waste of chemically processed timber (lignin). Importance of such R&D activity proves the award of the Ministry of the Environment of the Slovak republic in the category "Progressive Idea". Moreover, significance of such investigation has confirmed the teamwork with the Austrian scientists in a bilateral R&D project as well as organization of several international scientific workshops. The long-lasting collaboration with various outstanding European laboratories was awarded the Prize of the Slovak Academy of Sciences for International R&D cooperation. Results published in peer-reviewed journals underline the relevance of such research activity (glucan: *Cancer. Lett. 2003; 198: 153-60*; *Environ. Mol. Mutagen. 2003; 41: 28-36; Neoplasma. 2004; 51(6): 432-6; Neoplasma. 2006; 53(5): 434-9; Nutr. Cancer 2006; 56 (1): 113-22,;* lignin: *Biomass and Bioenergy: New Research. Brenes M.D. (editor), Nova Science*

Publishers, Inc., Hauppauge, N.Y., 2006, ISBN 1-59454-865-X, p. 169-200; Wood Res. 2006; 51 (2): 41-8; Nutr. Cancer - in press.). The last not least research activity was aimed at the mechanisms underlying the inter-individual variability in radiation susceptibility with emphasis on the single nucleotide polymorphism(s) in genes involved in the DNA repair and cell cycle regulation, and gene-gene interactions (*Neoplasma - in press*). Part of this research was focused on the genotype-phenotype interactions, i.e. on the impact of genetic variation on phenotypic expression. In line with the European research policy aimed at translation of discoveries in basic research into clinical application, a close cooperation was created between the research staff and the clinic, the National Cancer Institute. The benefit of this research might be potential diagnostic tools which could allow personal radiotherapy planning. In order to continue in such research, the scientific staff took part in preparation of several international proposals under the 5th and 6th FR (MARISEN, GEPMIS, and GENIRAD) which, unfortunately, had failed.

Laboratory of Molecular Immunology

Natural compounds – beyond the chemoprevention. Carcinogenesis is a multistep process of malignant transformation progressing towards uncontrolled proliferation, invasion and metastasis. Cancer risk can be reduced by eliminating or minimizing the exposure to the identified carcinogens or by the use of nutritional supplements and modified diets. Dietary pattern characterized by high intake of fresh fruits and cruciferous vegetables is associated with a reduced risk of renal cell, pancreatic, prostate and colorectal carcinomas. Isothiocyanates (ITCs), naturally occurring food components, inhibitors of phase I enzymes and inducers of phase II enzymes, are known as chemopreventive agents. Their precursors are constituents of cruciferous vegetables, which consumption is associated with a reduced incidence of cancer. Similarly, garlic and garlic supplements, most likely for their high content of the water- and lipid-soluble organosulphur compounds (OSC) have been considered to be one of the best disease-preventive food.

We demonstrate that ITCs treatment caused a significant G2/M phase cell cycle arrest in wide range of tumor cell lines tested. This arrest is associated with increased phosphorylation of histone H3 and H4 acetylation *(Neoplasma. 2006; 53(6):463-70).* The early effect of treatment is represented by intracellular decrease of reduced GSH amount and nuclear translocation of transcription factors *(J Agric Food Chem. 2006; 54(5):1656-62).* ITCs treatment induced expression of acute phase II enzymes, ABC transporters, disruption of microtubule network formation, G2/M arrest and mitotic catastrophe, ROS production, and involvement of MAPK pathways in their effects *(Biochem Pharmacol. 2005;69(11):1543-52, Anticancer Res. 2005;25(5):3375-86, Int J Oncol. 2005;27(5):1449-58).*Similarly OSC treatment affects basic cellular pathways involved in cell cycle, redox state, and mitochondrial transmembrane potential *(Neoplasma. 2006;53(3):191-9).*

We showed for the first time that combined treatment of cells with synthetic isothiocyanate E-4IB and chemotherapeutic drug platinum resulted in synergistic cytotoxic effect. Significant modulation of cellular signaling pathways in ovarian carcinoma cells were found *(Apoptosis 2006;11(8):1299-310)*. The enhanced cytotoxicity was due to increased intracellular accumulation of platinum induced by E-4IB co-treatment *(Br J Cancer. 2006; 95(10):1348-53).*

Apoptosis in radio- and multidrug-resistant cell lines. The current standard therapy of ovarian cancer patients consists of surgery and platinum-based chemotherapy. A common problem limiting treatment success in ovarian cancer patients is the development of resistance to chemotherapeutic agents and irradiation. Multiple mechanisms are likely to be involved. The key to sensitivity may well be the ability of tumor cells to engage the process of apoptosis induced by DNA damaging chemotherapeutic agents and irradiation. In our study we have found that all examined cell lines exhibited a dose-dependent G2/M arrest after irradiation. A strong correlation was observed between the G2/M arrest and apoptosis induction. The rate of apoptosis correlated with the stringency of the G2/M arrest. In cells showing a prolonged G2/M arrest the apoptotic response was the most pronounced. In the examined cell lines the G2/M arrest is an important

component of the pathway leading from irradiation-induced DNA damage to apoptosis *(Int J Oncol. 2003; 22(1):51-7)*.

Multidrug resistance (MDR), the principal mechanism by which many cancers develop resistance to chemotherapy drugs and is the major factor in the failure of many forms of anticancer therapy. It affects patients with a variety of blood cancers and solid tumors, including breast, ovarian, lung and lower gastrointestinal tract cancers. Many cytotoxic drugs that selectively target actively proliferating cells include diverse groups of anticancer compounds, such as anthracyclines, DNA alkylating agents, antimetabolities, intercalating agents, mitotic inhibitors, translational inhibitors, nucleoside analogues, microtubule inhibitors and also natural compounds flavonoids. Some of these compounds are capable to modulate/inhibit MDR accompanied with alterations of several intracellular processes. In this context we studied:

Alterations in viability, immunophenotype, cell cycle and in the experession of transmembrane glycoprotein (P-gp, 170-180 kDa, coded for MDR-1 gene), mediated by transport type of multidrug resistance (MDR) after treatments with selected flavonoids and antitumor drug doxorubicin were described. The expression of apoptotic biochemical markers (PARP, Bcl-2 proteins, p21WAF1/CIP1, cyt c) and several signal transduction enzymes (MAPK/MEK-1-ERK), involved in cell regulation and proliferation in leukemic sensistive (Pg-p-) a multidrug-resistant (Pg-p+) cells after treatments with natural compounds flavonoids (luteolin, apigenin, quercetin), the compounds with antioxidant, neuroprotective, cardioprotective and chemopreventive properties, was further evaluated *(Neoplasma. 2005;52(4):273-9).*

Combined effects of flavonoid resveratrol, as an effective natural compound with cytostatic, chemopreventive and antitumor effect, with several anti-tumor drugs (doxorubicin, cycloheximide, busulphan, gemcitabine and paclitaxel) with various chemical structure and effects on sensitive- (Pg-p-) and multidrug-resistant- (Pg-p+) cells were evaluated in relation to cell cycle and induced process of programmed cell death (apoptosis). In both cell variants, resveratrol induced accumulation of the cells in the S-phase of the cell cycle. In combination with antitumor drugs used, it induced different portions of apoptotic cells preferentially out of S-phase of the cell cycle *(Neoplasma. 2006;53(5):384-92).*

Tumor markers; Phenotypic patterns of leukemic and regenerating cells; Cell heterogeneity and minimal residual disease. Multiparameter immunophenotyping of bone marrow aspirates enables evaluation of leukemia therapy effectiveness by sensitive detection of malignant cells and thus minimal residual disease - MRD. However, following treatment the regenerating marrow and immunophenotype of the arising benign B-cell precursors (hematogones) in comparison to leukemic cells, mainly in acute lymphoblastic leukemia, are highly similar *(Neoplasma. 2005;52(6):502-509)*.Thus the analysis expression of hematogone antigens such as CD34, TdT, CD10, and CD20 to detect MRD is well-founded. Leukemia cells in precursor B-ALL (and in non-B ALL as well) have a heterogeneous antigenic profile due to the very large scale of aberrant phenotypes, whereas the benign precursor B-cells, hematogones, have an extremely high phenotypic stability unrelated to disease or therapy. We provided detailed definition of individual physiological maturation phases of B-lymphocytes (hematogones) in the course of BM regeneration in leukemia patients during and after treatment *(Cancer Treat Rev, 2007, submitted).* The possibility to distinguish, even at low frequencies, both leukemia cells from regenerating B-cell subpopulations during and after therapy will substantially improve the detection of residual leukemia.

By multiparameter flow cytometry we characterized in detail the phenotype of heterogeneous populations in various AML subtypes and identified the leukemia associated aberrant phenotype (LAP) in individual patients with acute myeloid leukemia (AML) for precise investigation of minimal residual disease *(Neoplasma. 2005;52(6):517-522).* For discrimination residual blasts during follow-up we found very important the identification of leukemia aberrant phenotypes and localization of blasts on CD45 versus SSC (side scatter) dot plots. Furthermore, due to phenotype heterogeneity of AML we found it necessary to monitor each subpopulation, even if it is present in low frequencies, as in several cases only one of subpopulations was observed to be responsible for the relapse of the disease. *(Neoplasma. 2006;53(6):500-506).* The

impact of phenotypic changes was investigated as well, as they may have a relationship to the treatment and correct assessment of MRD. Although we found in many patients changes in at least one antigen comparing diagnosis and the first relapse, at least one aberrant phenotype was constant in 92%. Therefore, due to antigen shifts preferably at least two or more aberrant phenotypes should be used for minimal residual disease detection.

The process of tumor development is frequently associated with altered HLA class I expression (down-regulation of classical class I antigens and ectopic expression of non-classical antigens). The highly controversial expression of non-classical HLA-G antigens in tumors has been the subject of our study. Using different methods we did not detect HLA-G antigens in any of 70 analyzed human tumor cell lines and of 50 hematopoietic samples freshly isolated from patients with different type of leukemia *(Leuk Res. 2003;27(7):643-8).* We have also investigated the effect of proteasome inhibitors (LLL, lactacystin and epoxomicin) on the constitutive expression of truncated HLA-G isoforms. In HLA-G transfectants we demonstrated that proteasome inhibitor LLL greatly enhances expression of HLA-G1 and -G2 transcripts as well as corresponding proteins *(Neoplasma 2003;50(5):331-8; Hum Immunol. 2004;65(2):157-62).*

A non-transformed diploid fibroblast cell line expressing the telomerase gene (NHF hTERT) was used to follow the formation and removal of H_2O_2-induced lesions. Using quantitative PCR, it was observed that these cells accumulate large amounts of mtDNA damage, which can be completely repaired after a 15-min treatment but not a 60-min treatment. Cell sorting experiments revealed that persistent lesions in the mtDNA correlate with loss of mitochondrial membrane potential, increased ROS generation, and cell death. Interestingly, we also show that the nDNA of the NHF hTERTs seems totally resistant to H_2O_2-induced damage, suggesting that SV40-transformation makes the nuclear genome more prone to oxidative injury. (*J Biol Chem. 2003 Jan 17;278(3):1728-34).*

Laboratory of Molecular Biology

General theme of our group is to understand the mechanism(s) of gene repression upon cellular growth arrest, as well as to understand the mechanism of programmed cell death (apoptosis).

Growth-arrest repression was studied using the human adenine nucleotide translocator-2 gene as a model. Using a combination of transfection, *in vivo* DMS mapping and *in vitro* DNase I mapping experiments, we have identified two protein binding elements (Go-1 and Go-2 elements) that were responsible for growth arrest of ANT2 expression in human diploid fibroblasts. These proteins have been purified and identified by MALDI-TOF MS as members of the NF-1 family of transcription factors. We have also purified the silencer element binding protein, which does not participate in growth-arrest repression but confers repression on the heterologous reporter gene, and identified it as a member of the nuclear family 1 (NF1) proteins. Thus, NF1 plays a major role in regulating ANT2 expression by modulating (repressing) the constitutive activator. The role of NF1 as an active growth arrest repressor is unique and to our knowledge we were the first to report it. *(J Biol Chem. 2003; 278(33):30624-33. Eur J Biochem. 2004; 271(9):1781-8)*

Apoptosis was studied using the yeast *Kluyveromyces lactis.* Yeasts are used as a tool to elucidate the molecular mechanism by which the pro-apoptotic proteins induce cell death. It is generally accepted that insertion of the pro-apoptotic protein Bax into mitochondrial membrane is a key step in triggering apoptosis. We asked whether the mitochondrial phospholipids, cardiolipin and its precursor phosphatidylglycerol, are necessary for the insertion of Bax into mitochondrial membrane and for its toxic effect. Our results suggest that these mitochondrial phospholipids play, to a certain extent, a role in the Bax-induced cell death. Apoptosis is also thought to occur after an increased production of reactive oxygen species (ROS). Mitochondria are the main producers of ROS. In yeast, contrary to mammalian cells, we did not find a direct correlation between ROS production and Bax effect. However, observed effect of individual respiratory substrates on Bax effect suggested that its toxicity is influenced by overall cellular metabolism (*Neoplasma. 2005; 52(6):441-9. FEBS Lett. 2005; 579(23):5152-6)*

Laboratory of Cancer Genetics

We have initiated molecular diagnosis of hereditary non-polyposis colorectal cancer (HNPCC) in Slovakia. This required establishing of several methods including microsatellite instability analysis, DNA sequencing of mismatch repair genes (*MLH1, MSH2, MSH6*) and Multiplex-ligation dependent probe amplification (MLPA) for detection of large genomic rearrangements. More than 100 of patients with colorectal cancer were evaluated for HNPCC diagnosis. We have confirmed HNPCC in 26 families and identified more than 50 asymptomatic mutation carriers, which are at risk to develop colorectal or other HNPCC associated cancer. During this mutational screening 13 novel HNPCC mutations were characterized *(Human Mutation 2003, 21(4), 449-453, Neoplasma 2006, 53(4), 269-276).* In addition, we have developed novel assay for detection of loss of heterozygosity by single nucleotide polymorphisms markers in *MLH1* and *MSH2* genes which may be potentially used for prediction of mutated gene and by this way facilitating the laborious mutational screening. To investigate the role of epigenetic changes in tumorigenesis of HNPCC tumors we evaluated DNA methylation status of the *MLH1* promoter as well as CpG-islands-methylation phenotype (CIMP) *(Cancer Biomarkers 2006, 2(1-2), 37-49).* Methylation profiles of the *MLH1* promoter observed in 18 tumors were not responsible for *MLH1* gene silencing. Similarly, no CIMP was found in hereditary cases, which can be utilized as molecular discriminator from widespread methylated sporadic unstable cancers *(Neoplasma.2007; accepted).* Several HNPCC tumors manifested deletions or insertions in microsatellites of *MRE11* and *RAD50* genes, which indicates the impairment of recombination in addition to DNA mismatch repair defect.

The screening of mutations in *BRCA1* gene of patients suspected from hereditary form of breast and ovarian cancer was established during 2003-2006 years. Patients from 130 Slovak suspected families were analyzed by single strand conformation polymorphism (SSCP) and consequent sequencing and the mutations were identified in 20 of them *(Neoplasma 2003, 50(6), 403-407; Her Can in Clin Pract 2006, 4(1), 7-11).* The presymptomatic diagnostics is gradually completed by mutation screening of the *BRCA2* gene *(Neoplasma 2006, 53(2), 97-102.).* Up to now the analysis of 72 families were finished. The pathogenic changes in *CHEK2* gene, which may induce the high risk of breast tumors were analyzed in cohort of 115 patients on the base of international collaboration. The most frequent alteration (1100delC) was not detected, but the new mutation, leading to long deletion in *CHEK2* gene was found *(JAMA 2006, 295(12), 1379-1388).*

Molecular diagnostics of hereditary form of colon cancer – adenomatous polyposis coli (FAP) was completed during the assessed period. By the techniques of SSCP, heteroduplex analysis (HDA) and sequencing of 410 persons from 162 suspected families from the whole Slovakia were analyzed. Mutations in *APC* gene, responsible for genetic predisposition to the disease, were detected in 62 patients from 34 families. Identified mutations are mostly registered in mutation databases, but another 11 new mutations were detected as well. Some clinically certified FAP families with undetected mutations in the *APC* gene were tested for germline mutations in the *TP53, K-ras, MYH* and *ß-catenine* genes and by the MLPA technique for detection of the long deletions *(Clin Genet 2006, 69, 183-186; Neoplasma 2007, accepted).*

Altogether for above tested diagnosis, the individuals with positive test results (164 persons) have a high risk (80 – 100%) to develop colorectal or breast/ovarian cancer, thus they were enrolled in the preventive health care program at specialized clinical departments. By this way, the chances to reveal the tumors in early and thus well treatable stages are rapidly increasing. The individuals with negative test results are rescued from psychical distress, which roots in their families over the generations. With the achieved results, we have contributed to lives savings, improvement of life quality of affected families and preservation of economical resources, otherwise used for treatment of patients in late stages of disease.

The specific ability of some intestinal bacteria to internalize epithelial cells of colon was observed as one of the potential factor of induction of colorectal cancer. Because of their suspected pathogenic influence, these bacteria were eradiated by probiotics bacteria

Enterococcus faecium M-74 *(Folia Microbiol 2005, 50(4), 443-447).* Complete eradication of intramuscular bacteria was observed in two followed patients. The positive effect of probiotics bacteria was manifested in the prevention of febrile neutropenia of patients after anticancer chemotherapy *(Neoplasma 2005, 52(2), 159-164; Support Care Cancer 2006, 14, 285-290).*

Antimetabolites are routinely used in treatment of haematological malignancies and colorectal carcinomas. Intracellular activation of these drugs is required for their cytotoxic and therapeutic effect. However, the extensive inactivation represents a significant limit for the therapeutic outcome of these agents. In order to enhance their cytotoxic/therapeutic effects, new conjugates, derivates and analogous were synthesized. In our work we evaluated the antileukemic activity of new synthesized substances. Various heterodinucleoside phosphates of 5-fluorodeoxyuridine (5-FdUrd), arabinofuranosylcytosine (*Int J Oncol 2004, 25, 357-364; Neoplasma 2007, 54, 68-74)* and araC conjugates indicating that are effective in inducing cell cytotoxicity and significantly increases the life-span of treated animals *(Anticancer Res 2003, 23, 3841-3846; Exp Oncol 2006, 28, 293-298).* We have investigated antitumor compounds which could provide a significant benefit for the treatment of human malignancies.

Laboratory of Molecular Genetics

Maintenance of the correct genetic information is crucial for all living organisms. DNA damage, if not repaired, can lead to mutations. Mutations are primary cause of hereditary diseases as well as cancer and may also be involved in aging. A variety of DNA repair mechanisms have evolved to protect the genome. Our long-term goal is to understand the nature of DNA repair in prokaryotes, lower and higher eukaryotes using for study the eubacteria, archae, yeast and mammalian cells as the model organisms.

The *Saccharomyces cerevisiae* Pso2 protein seems to function in processing of DNA ends during generation of DNA interstrand cross-link (ICL)-associated double-strand breaks (DSB). We have conducted a two-hybrid screen examining a possibility of interaction of Pso2 with all known DSB repair proteins in yeast. We found that Pso2 associates with none of the DSB repair proteins, suggesting that this protein likely does not act in the repair of ICL-associated DSB via cross-talk with DSB repair machinery. Therefore, its function in this process seems to be rather individual *(Neoplasma.2007;54(3):189-194).* In addition, we studied relation of Pso2 to other DNA repair proteins, Msh2 and Mgm101, which are mismatch repair and mitochondrial genome maintenance factors, respectively. For this reason, strains deleted for *PSO2*, *MSH2* and *MGM101* and all their combinations were constructed. In these strains, a number of biological processes have been examined. We found that Mgm101 is involved in the repair of nuclear oxidative DNA damage and that Pso2 has an overlapping role with both Msh2 and Mgm101 in ICL repair.

Oxidative damage to DNA is an important factor in developing many diseases including cancer. It also involves DSB, whose repair requires either homologous recombination (HR) or non-homologous end-joining (NHEJ). We have examined relative contribution of HR and NHEJ to cellular response after oxidative stress induced by hydrogen peroxide (H_2O_2), menadione (MD) and bleomycin (BLM) in *S. cerevisiae*. We found that H_2O_2 or MD exposure does not lead to DSB induction, suggesting that the toxic effects of these agents are mediated by other types of DNA damage. On the other hand, the basis of the BLM toxicity resides in DSB induction. Both HR and NHEJ act on BLM-induced DSB, although their relative participation in the process is not equal. It seems that the complexity and/or the quality of the BLM-induced DSB represent an obstacle for the NHEJ pathway, a fact that could have a great importance for the BLM-treated tumors *(DNA Repair.2006; 5(5):602-610).*

Selenium (Se) is an essential trace element which is important for many cellular processes. Se's bio-activity is mainly influenced by its chemical form and dose. The use of Se supplements in the human diet emphasizes the need to establish both the beneficial and detrimental doses of each Se compound. We have evaluated three Se compounds, sodium selenite (SeL), selenomethionine and Se-methylselenocysteine, with respect to their DNA damaging effects potentially manifested in *S. cerevisiae*. Only SeL manifested any significant toxic effects, which were accompanied with mutagenic effects in the stationary phase of growth.

The toxic and mutagenic effects of SeL are likely associated with the ability of this compound to generate DSB. We also found that SeL induced 1-4 bp deletions in the *CAN1* mutational spectrum. We propose that SeL is acting as an oxidizing agent producing superoxide and oxidative damage to DNA accounting for the observed DSB and cell death *(Carcinogenesis.2007; submitted).*

The recent discovery of an oxidative demethylation pathway of two minor DNA lesions (1-meA and 3-meC) generated by methylating agents provides the opportunity to examine the contribution of this damage and the role of the human AlkB protein to the toxic effect of alkylating drugs used in cancer therapy. Taking advantage of the physiological background of *S. cerevisiae* (which lacks the *alkB* gene) we studied the contribution of the *alkB* human genes to repair DNA damaged by the S_N2 alkylating agents. Our results indicate that hABH2 and hABH3 (AlkB like genes) have distinct roles in the repair of DNA lesions induced by these agents.

Nucleotide excision repair is a universal DNA repair mechanism found in all three kingdoms of life. It is a unique DNA repair pathway in its versatility to repair a broad range of DNA lesions. To understand the fundamental mechanisms of NER both in *Prokaryota* (by series of studies involving bacterial UvrABC machinery) and *Eukaryota* (study of human homologs XPB and XPD from an *Archaeon Pyrococcus abyssi*) we have characterized structurally, in extensive international collaboration, the human DNA repair helicase XPD by comparative molecular modeling and site-directed mutagenesis of the bacterial repair protein UvrB. We have identified the residues within UvrB that are important for efficient DNA binding and damage processing and proposed the mechanism of interactions between UvrA and UvrB and how the DNA binding and ATPase activity by UvrB domain 4 are regulated *(J.Biol.Chem.2003;278:5309-5316; J.Biol.Chem.2004;279:51574-51580; EMBO 2004; 3:2498-2509; J.Biol.Chem.2004;279: 45245-45256; J.Biol.Chem.2006;281:15227-15237).*

The ATP-dependent DNA helicase, a product of the *ERCC3/XPB* gene, is essential for transcription, DNA repair of UV-induced damage and p53-dependent apoptosis. The only six known mutations in humans with pleiotropic effects and serious impact on human health, with cancer and mental retardation as a consequence, limit its study. We have studied the unique set of nine hamster ERCC3 mutant cell lines. We have identified the new *ERCC3* gene mutations and connect them with UV- and oxidative damage cell survival, an ability to recover the transcription after DNA damage and repair DNA lesions. We have find that ERCC3/XPB helicase might be involved either in nucleotide excision repair (NER)-dependent removal of a fraction of the oxidative lesion or in NER-independent repair, i.e. transcription-coupled base excision repair, or additional DNA repair activities. DNA sequence analysis showed that *ERCC3* mutant cell lines most limited in their ability to recover RNA synthesis after oxidative damage produce ERCC3 protein truncated at its C-terminus due to mutations. Our results suggest that there might be a functional domain within the 5'-end of the ERCC3 protein, which is involved in the repair of oxidative damage. The repair is nucleotide excision repair-independent but involves the ERCC3 DNA helicase *(Neoplasma. 2003;50:389-395; Mutation Research.2006;593:177-186).*

To validate correlation between residual DNA repair foci and individual radiosensitivity of breast cancer patients (international collaboration) we have first analyzed relationship between dose response and time kinetics of residual foci obtained in human lymphocytes after gamma-irradiation *in vitro* and *in vivo*. *In vitro* results suggest that 53BP1/ γ-H2AX residual foci may constitute a useful bioassay for further assessment of radiosensitivity *in vivo.* The cases with prominent differences in radiosensitivity have been also tested to further verify the usefulness of residual foci assay as a biomarker for radiosensitivity. Using 11 cancer cell lines of various origins, cellular radiosensitivity and formation of residual DNA repair foci induced by ionizing radiation in the dose relevant for cancer therapy have been studied. Preliminary results indicate that DNA repair foci may be used for prediction of radiosensitivity in cancer therapy. The correlation between adverse effects of the cancer therapies according to RTOG criteria and residual DNA repair foci in lymphocytes of breast cancer patients undergoing radiotherapy have been analyzed in cooperation with National Cancer Institute, Department of Radiology *(Int.J.Radiat.Biol.2007;83(4):1-11).*

Laboratory of Molecular Oncology

Invasiveness an essential characteristic of malignant tumour cells can be profoundly influenced by stromal cells mainly fibroblasts. Since there exists reciprocal molecular exchange between the tumor mass and surrounding stromal cells the fibroblasts can hyperproliferate due to stimuli originating in transformed cells. As a consequence of local hyperproliferation of the fibroblasts multicell foci might be formed. These dense stromal structures can be mimicked *in vitro* by spheroids.

We have observed recently that clustering of human dermal fibroblasts within multicell spheroids is apparently a sufficient stimulus to trigger a series of spatio-temporal events leading to initiation and programmed progression of a non-apoptotic cell death *(Cell Death Differ. 11:183-195, 2004).* Dying cells developed necrosis-like morphological features and dramatic induction of several genes, including cyclooxygenase-2, was found in these decomposing cell clusters. Based on our findings concerning unique pattern of gene expression accompanying this novel type of cell death we came to a conclusion to name it nemosis *(Cancer Res. 65:9914-9922, 2005).*

We have found that the fibroblast spheroids committed to nemosis secrete factor(s) that stimulate migration of human tumor cells of epithelial origin e.g. carcinomas and melanomas. Therefore it was the purpose of the study to characterize more precisely set of genes which are upregulated in the system and contribute to enhanced invasiveness of tumor cells. Actually, we have identified hepatocyte growth factor (HGF) as one of the most abundantly produced growth factor by the dying cells.

We demonstrate that HGF is a distinct factor produced by stromal fibroblasts in nemotic cellular mass which in turn enhances invasiveness of carcinoma and melanoma cells. The present results, in accordance with existing literature data concerning involvement of necrosis-like cell death in enhancement of tumor progression, would explain at molecular level the inverse correlation that exists between this type of cell death and the survival of cancer patients. However obtained data might have clear implications for further development of our understanding of the HGF role in tumor progression and establishment of metastasis.

c-Myb is a DNA-binding transcription factor that plays a major role in the development of erythroid, myeloid, and lymphoid lineages of definitive hematopoiesis. The function of c-Myb as a regulator of hematopoiesis is achieved through transcriptional regulation of genes intimately involved in cellular processes such as proliferation, differentiation, and apoptosis. The observations that high-levels of wild-type c-Myb may lead to transformation of hematopoietic cells highlight the significance of understanding the mechanisms that control the activity of this oncoprotein. Posttranslational modifications such as phosphorylation, acetylation and ubiquitination play a central role in the regulation of c-Myb. Previously we have identified a mechanism of c-Myb regulation through covalent attachment of a Small Ubiquitin-like Modifier-1 (SUMO-1) to the negative regulatory domain of c-Myb. This modification dramatically increases the proteolytic stability and decreases the transactivation capacity of the c-Myb protein in cells growing under optimal growth conditions *(2002, JBC 15; 277(11): 8999-9009)*. Recently, a novel mechanism for the negative regulation of the transcriptional activator c-Myb under different types of stress was identified in our laboratory. We showed for the first time that environmental stresses, and to a lesser extent genotoxic stress, inactivate c-Myb through rapid covalent conjugation of SUMO-2/3 proteins to its negative regulatory domain. Stress-induced modification of c-Myb with SUMO-2/3 was also confirmed in hematopoietic cells at normal endogenous protein levels. *(2006; JBC 281(52): 40065-75).* This highlights the physiological relevance of this modification of c-Myb and raises the possibility that this novel post-translational modification is part of a regulatory pathway that controls the activity of c-Myb in cellular environments, such as hematopoietic tissues, where it plays critical roles. In addition, we have identified two c-Myb specific SUMO E3 ligases, PIAS3 and Pc2 that catalyze transfer of SUMO-2/3 proteins to target lysine residues of c-Myb. Our results significantly contribute to understanding of the biochemical pathways that control transcriptional and transforming activity of the c-Myb oncoprotein.

A prototypic vaccination approach to prevent disease caused by more complex retroviruses was tested. Rabbit BLV model was used to test whether simplified replication-competent bovine leukemia virus structural gene vector virus - BLV SGV (J. Virol. 71:1514-1520, 1997) can be used as a DNA preventive vaccine. Previously we have shown BLV SGV that lack *tax, rex*, RIII, and GIV, and the *cis*-acting Tax and Rex response elements is able to infect rabbits, induce virus immunological response without pathogenicity, while wild type BLV caused AIDS-like symptoms leading to death of the rabbits due to opportunistic infections. (AIDS 3:775-780 1989; J. Virol. 73:8160-8166, 1999). BLV SGV vaccinated and control rabbits were challenged with different amounts wild type virus producing cells at different period of time after DNA vaccination. Virus infection, pathogenicity, and immunogenicity were monitored by analysis of provirus DNA and presence of *tax* gene with PCR and Southern blot hybridization, and by seroconversion to BLV structural protein with Western blot. Chinchilla rabbits two years after vaccination with BLV SGV were found resistant to high dose virus challenge. They were challenged once more again two years after the first challenge. No pathologic signs were noticed up to four and half year observation period in one of the challenged animal. The similar dose of virus caused death of not vaccinated rabbit. Rabbits transfused intravenously with blood from vaccinated animals were partially protected against challenge. The results are consistent with the working hypothesis that simplified more complex retrovirus might be used as DNA vaccine preventing pathologic effects of more complex retroviruses. *(Virology. 329:434-439. 2004.)*

In order to asses the use of magnetic nanoparticles in cancer hyperthermic therapy we have evaluated their heating capabilities. In in vitro experiments they were exposed to an alternating magnetic field with frequency 3.5 MHz and induction 1.5 mT produced in three turn pancake coil. In in vivo experiments rats with injected magnetic nanoparticles were also exposed to an ac field. An optimal increase of temperature of the tumor to 44 degrees C was achieved after 10 minutes of exposure. Obtained results showed that magnetic nanoparticles may be easily heated in vitro as well as in vivo, and may be therefore useful for hyperthermic therapy of cancer. *(Med. Phys. 31, 2219-2221 (2004).)*

We have assessed the effect of combine cancer gene therapy with exogenous human tumor necrosis factor alpha (*hTNF*) in the following gene therapy models:

- *Escherichia coli* cytosine deaminase (*CD*) suicide gene on two human breast adenocarcinoma cell lines MDA-MB-361 and SK-BR-3.
- *Herpes simplex* thymidine kinase (*HSVtk*) suicide gene therapy system.on three human cancer cell lines MCF-7 (breast adenocarcinoma), U-118MGand 42-MG-BA (human gliomas).

The significant increase in apoptotic cells and decrease of cell proliferation in all tumor cell lines was observed using combine treatment with *hTNF* expression plus *CD*/5-FC suicide or combine treatment with *hTNF_* expression plus plus thymidine kinase/GCV suicide system . The additive neighboring cell killing effect due to the presence of bacterial *CD* and *hTNF_* gene or *HSVtk* and *hTNF_* therapeutic genes after activation of non-toxic prodrug was observed. (Neoplasma 2005;52 (4):344-351. Neoplasma (2006); 53 (5):353-362.,. Neoplasma (2006); 53 (6):478-484)

The influence of diet containing lyophilized Enterococcus faecium M-74 with organic selenium on tumor incidence in in Apc1638N transgenic mice carrying mutation in Apc gene was studied . Feeding of Apc1638N transgenic mice with enriched diet with probiotic components during 8 months have shown a minor therapeutic effect on the clinical manifestations in small intestine in comparison with control group. *(Neoplasma, 51, 341-344. (2004).)*

Novel germline mutation in the transmembrane region of *RET* gene close to Cys634Ser mutation associated with MEN 2A syndrome was discovered. Two mutations on the same allele of *RET* gene were revealed in the family with predisposition to multiple endocrine neoplasia type 2A (MEN 2A). The first mutation affects codon 634 and changes cystein to serine. The second, novel mutation was found in codon 641 at the transmembrane domain of the *RET* gene encoding

serine instead of alanine. Two mutations were present in close vicinity in patients' both germline and tumor DNA and were absent in DNAisolated from healthy family members and control blood donors. All MEN 2A affected familymembers suffered for medullary thyroid carcinoma, 2 out of 10 patients also for pheochromocytoma so far. No parathyroid gland alterations were observed in 3 investigated patients with two *RET* gene mutations. Analysis of four genetic polymorphisms in the *RET* gene showed higher incidence of polymorphisms of exon 11 and 15. The observed allelic imbalance in favour of mutated allele in pheochromocytoma, corresponded with higher expression of the *RET* gene. These observations confirm the multi factorial process leading to development of MEN 2A syndrome. *(J. Mol. Med. 2005;83(4):287-95.*

Human adipose tissue-derived mesenchymal stem cells (AT-MSC) are considered to be a promising source of autologous stem cells in personalized cell-based therapies.Tumor tracking properties of mesenchymal stem cells provide an attractive opportunity for targeted transgene delivery into the sites of tumor formation. We established techniques for isolation and characterization of mesenchymal stem cells derived from human adipose tissue and bone marrow. In *in vitro* and *in vivo* experiments using nude mice we proved that adipose tissue derived human mesenchymal stem cells mediated prodrug cancer gene therapy. Mesenchymal stem cells derived from adipose tissue were found to be suitable delivery vehicles for prodrug converting gene and show their utility for a personalized cell-based targeted cancer gene therapy. *(Cancer Research, 2006 {in revision}).*

Additional experiments were started in attempt to enrich the human tumor cells in cell lines for cancer stem cells. Properties of normal and cancer stem cells were summarized in *Neoplasma 2005;52 (6) 435-440.*

3. Concept of Research and Development activity of the Cancer Research Institute SAS for the next four years

(The concept was compiled and edited by the head of Scientific Board K. Luciakova, PhD, DSc.)

Cancer is caused by loss of the normal controls that regulate cell proliferation, differentiation and cell death. Aberrant transcription is a one of the key events leading to cancer development. Such events are often the earliest detectable changes, occurring long before any pathological changes and can have great diagnostic value. Another significant feature of normal cell development is it's response to extracellular and environmental signals and how the cell deals with inappropriate replication, transcription and/or translation. Therefore, it is of greatest importance to study how processes regulating normal cell growth and division are controlled and how they interact with each other. By understanding these processes we hope to find ways of exploiting the mutations which occur in cancer cells to make anti-cancer therapies more effective. Identifying the molecular changes involved in the early stages of cancer offers great potential for improved diagnostics and therapeutics.

The initial reaction of a cell to DNA damage is to repair it. The importance of DNA repair pathways for human health is demonstrated by the existence of several genetic disorders associated with defects in DNA repair or responses to DNA damage. Since double-strand breaks (DSB) can initiate processes leading to mutagenesis, tumorigenesis and death, their repair is essential to maintain genome stability and cell viability. The main pathway for the repair of DSB in mammals is non-homologous end-joining (NHEJ), in which the DNA ligase IV/XRCC4 complex (LX) is the key player. Recently, nine LIG4 patients have been reported, each with hypomorphic mutations in DNA ligase IV and one with two linked polymorphisms. Some of the mutant and polymorphic changes were already characterized *in vitro*, although *in vivo* data are rather limited due to a lack of sensitive *in vivo* assays in

mammals. We intend to further characterize impact of the mutant and/or polymorphic changes on LX function *in vivo*. This will be achieved by expression of the mutant and/or polymorphic LX in *Saccharomyces cerevisiae* and by monitoring of efficiency and accuracy of DSB rejoing in well-defined systems. Moreover, impact of mutant and/or polymorphic LX on chromosomal instability will be examined.

Nucleotide excision repair (NER) is able to repair large variety of DNA lesions. However, with increasing levels of DNA damage the cells switch from DNA repair to cell cycle arrest or apoptosis. Apoptosis prevents clonal expansion of cells in which unrepaired damage would lead to mutations and carcinogenesis. Major challenge is to understand the molecular mechanisms of damage recognition process which is impossible without structural information and structure-function analysis of the proteins involved. To understand the molecular mechanisms of DNA repair and apoptosis we plan to carry the structural and functional analyses of two DNA helicases – XPD and XPB, which are involved both in DNA repair and apoptosis. Structural analysis of these proteins will help to understand the molecular mechanisms of these DNA helicases during NER as well as the nature of their defect in patient and lead to a progress in targeting the therapy.

Cancer may be viewed as an inability of cells to terminally differentiate. The mechanism(s) by which gene expression is repressed in cells entering the G0 is poorly understood. 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. Aim of our future studies shall focus on the molecular mechanism by which NF1 inhibits expression of ANT2 gene and how this function is integrated into existing signaling pathways. Particularly, we shall study integration of NF1 into the transforming growth factor-β signaling pathway and Smad-related pathways. These studies will include the use of specific inhibitors against the TGF-β and MAP kinases, the siRNA methods for silencing individual Smad and NF1 proteins and mutation analysis of predicted DNA binding elements.

Histone deacetylase inhibitors show potency as promising antitumor agent with several drug candidates currently in clinical trials. In vivo studies histone deacetylase inhibitors are potent angiostatic agents. Histone acetylation/deacetylation has been correlated with chromatin assembly, DNA repair as well as replication timing. In addition to histones, many cytoplasmic and nuclear proteins can be reversibly acetylated, influencing protein stability, protein–protein interactions, protein localization, or DNA binding. Our data suggest that histone deacetylation and histone deacetylases play a role in lipid metabolism. Cholesterol and lipid homeostasis is achieved through the action of a complex regulatory network (regulome) 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 cholesterol metabolism genes 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. We will develop a rational design of affinity ligands for HNF-4α based on the analysis of their 3D-structures.

Apoptosis (programmed cell death) plays an important role in many physiological processes and its miss-regulation is linked to serious diseases. Since it is known that inhibition of cell death mechanisms is a common event in tumor development, we aim to understand the factors regulating programmed cell death in cells. Moreover, successful chemo- and radiotherapy of cancer depends, to some extent, on the ability of tumor cells to undergo apoptosis. Our research focuses on understanding the molecular mechanisms which control the induction of apoptosis and involvement of mitochondria in this process. We shall continue to study the molecular mechanism of Bax-induced apoptosis using the yeast *Kluyveromyces lactis* as a model. Specifically, we shall study the effect of Bax expression

and mechanism of its action on the fission and fusion of mitochondria, as well as on the structure of cytoskeleton. These studies will involve construction of strains with deleted genes important for fusion and fission of mitochondria. The effect of Bax expression in such mutant strains will help to understand how mitochondrial dynamics is involved in apoptosis.

Another mechanism for cell death is necrosis. It has been assumed that necrosis is not regulated. We have discovered a highly regulated process which we have named nemosis. Nemosis represents a novel type of mesenchymal cell activation that induces a massive proinflammatory, proteolytic and growth factor response and terminates in programmed necrosis. Nemosis may be a critical process in the tumor-stroma interaction leading to tumor progression. Our research will focus on clarification of the role of nemosis in the processes like organ regeneration involving skin, heart and spinal cord. For this purpose human organ cultures and animal model systems will be employed and complemented with advanced molecular biology techniques as high-density microarrays, PCR and complex set of proteomic methodology. Nemosis will be used as a tool to revise Warburg effect as a prospective pathway for anti-tumor treatment.

Based on our experience with human mesenchymal adult stem cells, we plan to use human mesenchymal stem cells as vehicles for targeted tumor gene therapy. Knowledge of the mesenchymal stem cell – cancer cell interactions is a prerequisite for future use of these cells in clinical applications for the inherited and acquired diseases in general, and personalized gene therapy of cancer in particular. We shall study human mesenchymal stem cell transformation by chemical carcinogens and try to isolate cancer stem cells from established tumor cell lines in order to characterize them. Isolation and identification of cancer stem cells in solid tumors has important implications for the studies to develop targeted treatment of malignancies. Bulk of tumor mass is composed of cell clones differing in respect to proliferation, differentiation and ability to initiate tumor. Experimental evidence for the cancer stem cells theory has shown that tumors may originate from transformed stem cells and/or from their incorrectly differentiated progenitors. Cancer stem cells are responsible for the tumor growth maintenance. Cytotoxic chemotherapy or radiotherapy mostly kills rapidly dividing tumor cells but cancer stem cells survive due to their relative high drug resistance and replication quiescence. It is anticipated that cancer stem cells are also responsible for tumor reoccurrence even many years after the initial treatment. Therefore any long-term effective and/or successful therapy must target the quiescent cancer stem cells. In order to find treatment modalities to destroy cancer stem cells, we intend to establish methods for their isolation, propagation and culture for detailed molecular characterization.

Stem cells possess both self-renewal capabilities and the ability to generate an organ-specific, differentiated repertoire of cells. The epithelial-mesenchymal transition is a process characterized by loss of epithelial characteristics and gain of mesenchymal attributes in epithelial cells. It has been associated with physiological and pathological processes requiring epithelial cell migration and invasion. Increasing number of stemness markers inappropriately expressed in tumors (as well as in tumor cell lines) detected in all steps of tumor development allows characterization and isolation of such tumor stem cells for further, detailed, molecular studies. Studies of tumor stem cells provide new insights into the phenomena such as therapy-induced multidrug resistance, intracellular signaling pathways activation, expression of HLA-G and differentiation-specific antigens, epigenetic gene regulation and assessment of role of paracrine signaling in different microenvironment milieu. Cell cultivation on low adhesion hydrogel surfaces and at low-shear modeled microgravity forces cells to remain in suspension and to form 3D spheroids. This will allow the assessment of growth regulation and expression of typical nonhemopoietic tumor stem cells antigens such as CD24, CD44, CD133, CD326, and ABCG2 resembling the in vivo conditions. Multiparameter flow cytometric analysis with optimal combinations of monoclonal antibodies will be applied to analyze multiplex cellular “barcoding” labeling. Fluorimetry in 96-

and 384-well format will be applied for “in-cell western blotting” using IR spectra of quantum dots labeled antibodies specific for different types of posttranslational protein modifications. It represents a complementary method to western blotting suitable for rapid screening of large amount of samples to analyze components of intracellular signaling pathways.

It is generally accepted that the effectiveness of antineoplastic therapy can be increased by using a combination of antineoplastic agents with different mechanisms of action such as drugs with conventional and targeted mechanisms. Our studies focus on how targeted agents (valproic acid, decitabine, gossypol and zactima) in combination with conventional antineoplastics (anthracyclines, alkylation compounds, taxanes, antimetabolites, and topoisomerase I a II inhibitors) affect the cytotoxicity and chemotherapy. Our goal is to receive synergism in cytotoxicity and chemotherapy. We plan use the conventional drugs in primary therapy (to cytoreduction of leukemia cells) and targeted drugs will be used in adjuvant therapy (to induce a permanent remission) or in a therapy of relapse. Evaluation of pre-clinical experiments should lead to the best drug combinations and these will be suggested for clinical trials.

To prevent and improve treatment of cancer, it is of utmost importance to understand the cellular and molecular mechanisms underlying the process of neoplastic transformation. We shall continue our ongoing research devoted to the molecular and cellular mechanisms of chemical carcinogenesis with stress on DNA damage pattern detection in cells exposed to single chemical substances and simple mixtures using various cytological (chromosomal aberrations, micronucleus assay) and biochemical (the comet assay, alkaline elution, hydroxyapatit chromatography) techniques including DNA sequencing. In addition, the role of signaling pathways in the neoplastic transformation shall be studied by western blot analysis using specific antibodies against the known members of MAP kinase pathways and fluorescent approaches (scrape-loading technique) shall be applied to study the modulation of gap junctional intercellular communication by chemical compounds. A great attention shall be paid to the molecular and cellular mechanisms underlying the chemopreventive potential of natural substances with emphasis on their potential use as supplements in cancer therapy. Part of the research activity shall be aimed at the mechanisms responsible for inter-individual variability in radiation susceptibility with emphasis on translation of basic discoveries to clinical applications. Specifically, we shall study the role of genetic polymorphism in the variability of radiation susceptibility by PCR and PCR-based restriction fragment length polymorfism (PCR-RFLP).

Residual DNA repair foci assay as a biomarker for radiosensitivity of breast cancer patients may be used for prediction of individual radiosensitivity and optimization of cancer therapy. The main objective of predictive testing is to tailor radiotherapy prescriptions to the individual patient. If the individual risk of radiation complications is known before therapy, the risk could be lowered in the small proportion of highly sensitive patients by dose reduction and conversely, radiation dose and possibly the chance of cure could be increased in normal and resistant patients.

Early diagnostics of predisposition to cancer is an important feature in managing the disease. We have developed molecular diagnostics of several hereditary forms of cancer. Namely, we have established techniques to detect predisposition to familial adenomatous polyposis (FAP), hereditary non-polyposis colorectal cancer (HNPCC), breast cancer and multiple endocrine neoplasia, type 2. Besides the direct sequencing of genes involved in the above mentioned cancers, we have developed a loss of heterozygosity (LOH-SNaP) assay for efficient detection of genetic events at MLH1 or MSH2 loci leading to mismatch repair deficiency and tumor formation in individuals with HNPCC. We shall continue in developing more powerful techniques to detect mutations in DNA. Complementary to the genetic factors in cancer development, we also study the epigenetic factors. The long-term aim of many laboratories is the mapping of methylation profile of silenced genes in different types of

cancer which may help to detailed characterization of their features, malignant potential or sensitivity to therapy. We have introduced qualitative methods for evaluating the methylation status for colorectal and breast cancer (MSP and genomic sequencing of bisulfite-modified DNA). Our further contribution to the epigenetic events in cancer development is to introduce new sensitive molecular markers for cancer cells in general, and for more exact classification of colorectal and breast cancers in particular. These molecular markers may also be used for the evaluation of epigenetic therapy. In collaboration with Technical University, Bratislava we validated isothiocyanate compound (E4-IB ITC) which may serve as a potent anti-cancer chemopreventive agent. In respect to recent advances in nanomedicine which offers the possibility of new and intriguing opportunities in nanoparticle-based treatment of diseases, we would like to develop nanoparticles with encapsulated E4-IB which may reduce the cancer risk in individuals with HNPCC. Our previous data confirmed the specific ability of some intestinal bacteria to internalize epithelial cells in the colon of colorectal cancer patients. We shall continue using probiotics bacteria *Enterococcus faecium* M-7 to eradicate intracellular bacteria in the patients with familial adenomatous polyposis (FAP) and the patients with spontaneous polyps, adenomas and carcinomas. The positive effect of these probiotics bacteria, manifested in the prevention of febrile neutropenia of patients after anticancer chemotherapy, will be administered to a large cohort of leukemic patients.

Recent advances in flow cytometry employing polychromatic analysis and hierarchical clustering analysis can be used for detailed classification of cell subpopulations. Such approach will confirm the diagnosis of individual leukemia patients separating them into prognostic groups for correct therapeutic protocols. Moreover, it allows reliably discriminate leukemic, regenerating and normal hematopoietic cells even if present in minute frequencies. It is feasible to monitor the minimal residual disease and early relapse and increase the sensitivity threshold of detection methods.

In order to achieve future proposed objectives we plan to accomplish the following:

- To strengthen the collaboration with our clinical partners
- To participate in the creation of national tumor tissue bank with international cooperation with the Organization of European Cancer Institutes in 7th FP
- To establish high-throughput multiplex analytic techniques
- To further exploit the nanoparticles in early diagnosis and therapy
- To stimulate the mutual mobility scientific exchange

III. Partial indicators of the main activities:

1. Research output

i. 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

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ii. List of monographs/books published abroad

N/A

iii. List of monographs/books published in Slovakia

[1] BABUŠÍKOVÁ O. Imunitný systém – jeho zložky a funkcie. Imunitný systém a nádory. Liga proti rakovine SR, 2003, s. 26.

[2] PLEŠKO, I. - OBŠITNIKOVÁ, A. - ŠTEFAŇÁKOVÁ, D. - KUZMA, I. - CUNINKOVÁ, M. -HLAVATÁ, B. - BENEŠOVÁ, A. - KOMPAUEROVÁ, H. - RÁKOCZOVÁ, E. - ONDROVIČOVÁ, M. - MADŽOVÁ, J. - POKRIVČÁKOVÁ, M. - ŠPANKOVÁ, A.: Incidencia zhubných nádorov v Slovenskej republike 2000. Bratislava, K.F.Print 2003, s. 210.

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[5] ALTANER Č: Je rakovina dedičná? ISBN 80-89201-00-8 vydaná Ligou proti rakovine, 2004.

[6] ALTANER Č: Prečo fajčenie cigariet spôsobuje rakovinu ISBN 80-98201-01-6 vydaná Ligou proti rakovine, 2004.

[7] ALTANER Č: Vplyv stravy na vznik a prevenciu nádorového ochorenia ISBN 8089201075 vydaná Ligou proti rakovine, 2004.

[8] PLEŠKO, I. - ONDRUŠOVÁ, M. - ŠTEFAŇÁKOVÁ, D. - KUZMA, I. - MADŽOVÁ, J. - POKRIVČÁKOVÁ, M. a kol. *Incidencia zhubných nádorov v Slovenskej Republike 2002.* Bratislava: Ústav zdravotníckych informácií a štatistiky, 2005. 207 s.

[9] PLEŠKO, I. - BARÁKOVA, A. - DUDOVA, M. Epidemiológia zhubných nádorov v Slovenskej republike, 1971-2003. Bratislava: Ústav zdravotníckych informácií a štatistiky a národný onkologický register, 2005. 75 s.

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

Sequences published in database GenBank™:

- Markus J, Feikova S, Sramko M, Wolff L and Bies J: Mus musculus M4MBT (M4mbt) RNA, complete cds. GenBank® entry (AY237000)
- Markus J, Feikova S, Sramko M, Wolff L and Bies J: Mus musculus M4MBT variant B (M4mbt) mRNA, complete cds; alternatively spliced. GenBank® entry (AY237001)
- Markus J, Feikova S, Sramko M, Wolff L and Bies J: Mus musculus M4MBT variant C (M4mbt) mRNA, complete cds; alternatively spliced. GenBank® entry (AY237002)

Number of pathogenic mutations in hMLH1 and hMSH2 genes published on-line in Database of InSIGHT (http://www.insight-group.org) by Bartosova Z. et al. and Zavodna K. et al.

v. 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	2003			2004			2005			2006			total			
	number	No. / FTE	No. / salary budget	number	No. / FTE	No. / salary budget	number	No. / FTE	No. / salary budget	number	No. / FTE	No. / salary budget	number	averaged number per year	av. No. / FTE	av. No. / salary budget
chapters in monographs, books published abroad	9	0.24	0.46	1	0.03	0.05	0	0.00	0.00	4	0.09	0.18	14	3.5	0.09	0.17
chapters in monographs, books published in Slovakia	8	0.21	0.41	4	0.11	0.20	0	0.00	0.00	0	0.00	0.00	12	3.0	0.08	0.15
CC publications	48	1.28	2.45	52	1.39	2.60	33	0.89	1.58	56	1.21	2.57	189	47.3	1.19	2.29
scientific publications indexed by other databases (specify)	0	0.00	0.00	0	0.00	0.00	1	0.03	0.05	1	0.02	0.05	2	0.5	0.01	0.02
scientific publications in other journals	21	0.56	1.07	22	0.59	1.10	18	0.49	0.86	14	0.30	0.64	75	18.8	0.47	0.91
publications in proc. of international scientific conferences	22	0.59	1.12	5	0.13	0.25	14	0.38	0.67	5	0.11	0.23	46	11.5	0.29	0.56
publications in proc. of nat. scientific conferences	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	0	0.0	0.00	0.00
active participations at international conferences	65	1.73	3.31	68	1.81	3.40	82	2.22	3.92	104	2.25	4.77	319	79.8	2.02	3.87
active participations at national conferences	30	0.80	1.53	17	0.45	0.85	18	0.49	0.86	50	1.08	2.29	115	28.8	0.73	1.40

vi. Renormalized publications[2]

Renormalized publications = number of CC publications in the given year times authorship's portion of the Organisation times the journal impact factor in 2005 divided by the median impact factor in the research field

Renormalised publications	2003			2004			2005			2006		
	number	No. / FTE	No. / salary budget	number	No. / FTE	No. / salary budget	number	No. / FTE	No. / salary budget	number	No. / FTE	No. / salary budget
Renormalized publications	21.018	0.56	1.07	32.245	0.86	1.61	26.168	0.71	1.25	34.822	0.75	1.60

vii. Standard manuscript page count[3]

Standard manuscript page count	2003			2004			2005			2006		
	number	No. / FTE	No. / salary budget	number	No. / FTE	No. / salary budget	number	No. / FTE	No. / salary budget	number	No. / FTE	No. / salary budget
page count	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0

viii. List of patents and patent applications

N/A

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

In 1976, the population-based National Cancer Registry covering the whole of Slovakia was established in the Cancer Research Institute of Slovak Academy of Sciences. From that time we participate on the collection of cancer incidence data and on

[2] This information is required only from the Organisations of the Section 2 of the Slovak Academy of Sciences.
[3] This information is required only from the Organisations of the Section 3 of the Slovak Academy of Sciences.

their analysis. The data are frequently appearing in the European cancer journals and epidemiological monographs. Whenever the cancer epidemiological data from Slovakia are published, or mentioned, these are outputs of our Institute, despite that the Institute is not acknowleged.

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	2002			2003			2004			2005			total			
	number	No. / FTE	No. / salary budget	number	No. / FTE	No. / salary budget	number	No. / FTE	No. / salary budget	number	No. / FTE	No. / salary budget	number	averaged number per year	av. No. / FTE	av. No. / salary budget
Web of Science	369	9.8	18.8	384	10.2	19.2	433	11.7	20.7	453	9.8	20.8	1,639	409.8	10.4	19.9
(specify Database 1)	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
(specify Database 1)	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
in monographs, conf. proceedings and other publications abroad	7	0.2	0.4	1	0.0	0.1	8	0.2	0.4	4	0.1	0.2	20	5.0	0.1	0.2
in monographs, conf. proceedings and other publications in Slovakia	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

[1] 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. **citations: 63**

[2] Saparbaev, M. - Kleibl, K. - Laval, J. E.coli, S. cerevisiae, rat and human 3-methyladenine DNA glycosylase repair 1,N6-ethenoadenine when present in DNA. In Nucleic acids research. Vol. 23 no. (1995), p. 3750-999. **citations: 38**

[3] Theis, K. - Chen, P. - Škorvaga, M. - Van Houten, B. - Kisker, C. Crystal structure of UvrB, a DNA helicase adapted for nucleotide excision repair. In EMBO journal. Vol. 18 no. (1999), p. 6899-6907. **citations: 38**

[4] Pastoreková, S. - Zavadova, S. - Kostal, M. - Babušíková, O. - Zavada, J. A novel quasi-viral agent, MATU, is a 2-component system. In Virology. Vol. 187 no. 2 (1992), p. 620-626. **citations: 31**

[5] Sier, C. - Stephens, R. - Bizik, J. - Mariani, A. - Bassan, M. - Pedersen, N. - Frigerio, L. - Ferrari, A. - Dano, K. - Brunner, N. - Blasi, F. The level of urokinase-type plasminogen activator receptor is increased in serum of ovarian cancer patients.. In Cancer research. Vol. 58 no. (1998), p. 1843-1849. **citations: 29**

[6] Collins, A. - Horváthová, E. Oxidative DNA damage, antioxidants and DNA repair: applications of the comet assay.. In Biochemical society transactions. Vol. 29 no. part 2 (2001), p. 337-341. **citations: 24**

[7] Zaid, A. - Li, R. - Luciaková, K. - Baráth, P. - Nery, S. - Nelson, B. On the role of the general transcription factor Sp1 in the activation and repression of diverse mammalian oxidative phosphorylation genes. In Journal of bioenergetics and biomembranes. Vol. 31 no. (1999), p. 129-135. **citations: 22**

[8] Sigler, K. - Chaloupka, J. - Brozmanová, J. - Stadler, N. - Hofer, M. Oxidative stress in microorganisms - I Microbial vs. higher cells - Damage and defenses in relation to cell aging and death. In Folia microbiologica. Vol. 44 no. 6 (1999), p. 587-999. **citations: 21**

[9] Horváthová, E. - Slameňová, D. - Hlinčíková, L. - Mandal, T. - Gábelová, A. - Collins, A. The nature and origin of DNA single-strand breaks determined with the comet assay. In Mutation research - Genetic toxicology and environmental mutagenesis. Vol. 409 no. 3 (1998), p. 163-171. **citations: 21**

[10] Kolarov, J. - Kolarova, N. - Nelson, N. A third ADP/ATP translocator gene in yeast.. In Journal of biological chemistry. Vol. 265 no. 265 (1990), p. 12711-12716. **citations: 21**

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

[1] Bies Juraj – 164

[2] Luciaková Katarína – 145

[3] Slameňová Darina – 118

[4] Horváthová Eva – 109

[5] Sedlák Ján – 108

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

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

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

i. 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] The Institute together with the St. Elisabeth Oncological Institute in Bratislava constitute the Comprehensive Cancer Center in Slovakia, which is a member of the Organization of European Cancer Institutes (OECI)

[2] The Institute is Member of National Cancer Institute Information Associates Program (USA)

[3] The research activities on hereditary non-polyposis colorectal cancer led to invitation (by J. Jiricny, IMCR, Switzerland) to participate in consortium of project funded in 5FP of European Union

[4] The research activities on mutagenesis and carcinogenesis of potentially dangerous environmental compounds led to invitation (by P. Farmer, University of Leicester, UK) to participation in consortium of project funded in 5thFP of European Union

[5] The research activities on transcriptional regulation led to invitation (by M. Crestani , University of Milan, Italy) to participation in consortium of project funded in 6thFP of European Union

[6] The researches of the institute were invited to participate in further 8 project proposals submitted in the FP of EU which were evaluated but not funded.

[7] The research activities of I. Pleško's group became a part of number of European projects (EUROCARE, EUROCHIP, EUROCIM, EUROTIS, etc.).

[8] The institute participated on the several official joint projects with USA, Denmark, Austria and Czech Republic including funding.

[9] The institute has number of collaborations with research laboratories in Europe (e.g in Sweden, Norway, Finland, Germany, Belgium, Denmark, France, UK, Switzerland, Italy, Austria, Hungary, Czech Republic) resulting in number of joint publications.

[10] The researchers from the institute are invited to host in European research laboratories. Such invitations came from UK, Austria, Sweden, Italy, Finland, France, and Norway.

[11] Several researchers from the institute were invited to host in research laboratories in USA and further collaborate with them.

[12] The institute was able to organize several international conferences including a major international conference "Cancer2006" with participation of attendees from 13 different countries including USA.

[13] The international CC journal NEOPLASMA is published by the institute already for 54 years

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

[1] 2nd International meeting on yeast apoptosis (Smolenice, 2003)

[2] Inter-field Slovak-Czech toxicology conference (Bratislava, 2004)

[3] Protection of genotoxic effects of carcinogens by micronutrients (2004)

[4] Autumn workshop: Genetic toxicology and cancer prevention (Bratislava, 2004)

[5] Fourth DNA repair workshop (Smolenice, 2004)

[6] Final bilateral Slovak-Austrian meeting "Protection of genotoxic effects of carcinogens by micronutrients" (Bratislava, 2005)

[7] XXIInd international conference on yeast genetics and molecular biology (Smolenice, 2005)

[8] Autumn workshop: Genetic toxicology and cancer prevention (Bratislava, 2005)

[9] Cancer 2006: From molecular biology processes to tumor-tailored therapy (High Tatras, 2006)

[10] Autumn workshop: Genetic toxicology and cancer prevention (Bratislava, 2006)

iii. List of international journals edited/published by the Organisation

[1] NEOPLASMA, which is the only cancer specialised CC journal published in Central Europe (meaning Czech Republic, Poland, Hungary and Slovak Republic)

iv. List of edited proceedings from international scientific conferences and other proceedings

[1] Protection of genotoxic effects of carcinogens by micronutrients. Bratislava 2004 (ISBN 80-969231-3-7)

[2] Autumn workshop: Genetic toxicology and cancer prevention. Bratislava 2004 (ISBN 80-969136-9-7)

[3] Final bilateral Slovak-Austrian meeting Protection of genotoxic effects of carcinogens by micronutrients. Bratislava 2005 (ISBN 80-969398-1-5)

[4] Autumn workshop: Genetic toxicology and cancer prevention. Bratislava 2005 (ISBN 80-969398-0-7)

[5] Cancer 2006: From molecular biology processes to tumor-tailored therapy. High Tatras 2006 (ISBN 80-969541-8-0)

[6] Autumn workshop: Genetic toxicology and cancer prevention. Bratislava 2006 (ISBN 80-969524-5-5)

[7] Fourth DNA repair workshop. Smolenice 2004

- **National position of the Organisation**

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

[1] Use of Cancer Genomics to Improve the Human Population Health

[2] Centre of Molecular Medicine of the Slovak Academy of Sciences

[3] Functional food-influenced gastrointestinal tract – in vivo and in vitro models

[4] Cytotoxic drugs and ionizing radiation-induced apoptosis and necrosis in human chemo- and radio-resistant neoplastic cell lines

[5] Particular response markers in men occupationally exposed to radiation: cellular damage response and apoptosis

[6] The role of mitochondria in the life and death of a cell

[7] Prototypic preventive DNA retrovirus vaccine against more complex retrovirus tested on bovine leukemia virus rabbit model

[8] Identification of the proteins involved in the regulation of c-Myb proteolysis

[9] Study of posttranslational modification of the c-Myb oncoprotein by the covalent attachment of SUMO-2/3 proteins

[10] Biological and molecular aspects of human melanoma progression: The effects of nonsteroidal anti-inflammatory drugs on invasiveness of tumor cells assayed by three-dimensional organotypic culture system

[11] Mutation of *RET* proto-oncogene - its implication in connection of thyreoid tumor incidence in diagnostic and prevention of thyreoid gland tumors

[12] Analysis of genetic alterations associated to hereditary non-polyposis colorectal cancer

[13] Modulation of genotoxic impairmens on the level of chromosomes, total DNA and tumor suppressor gene p53 by natural antioxidants; study on mammalian cells cultured in vitro and ex vivo

[14] The biological effects of a binary mixture of benzo(a)pyrene and 7H-dibenzo[c,g]carbazole on mammalian cells cultivated in vitro

[15] The role of genotoxic and epigenetic mechanisms in tissue and organ specificity of chemical carcinogens; mammalian cells cultivated in vitro as a model system

[16] Modulation of biomarkers related to carcinogenic processes in vitro and in vivo by natural cyclic triterpenes possessing potential chemopreventive properties

[17] A possible role of the Snm1/Pso2 protein in DNA double-strand break repair in the yeast Saccharomyces cerevisiae

[18] Contribution of homologous recombination and non-homologous end-joining to DNA double-strand break repair after oxidative stress in the budding yeast Saccharomyces cerevisiae

[19] Adenine nucleotide translocase as a model for biogenesis of mitochondria

[20] Study of new prognostic markers and therapeutical approaches in gynaecologic malignancies: factors and pathways influencing course (progress) of the disease and antitumour immunity

[21] Study of the role of the hamster ERCC3/XPB protein in the nucleotide excision repair and transcription

[22] The study of chemopreventive and chemotherapy modulating activities of the biologically active substances

[23] Chemotherapy and multidrug resistance (MDR): modulation of resistance and relationship to the regulation of apoptosis in human cancer cells.

[24] The role of intraepithelial bacteria in processes of colorectal carcinogenesis

[25] The study of mutations in genes participating in the process of tumorigenesis of the colon polyposis

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

[1] Autumn workshop: Genetic toxicology and cancer prevention (Bratislava, 2003)

[2] XL. Bratislavian Oncological Days (Bratislava, 2003)

[3] XLI. Bratislavian Oncological Days (Bratislava, 2004)

[4] XLII. Bratislavian Oncological Days (Bratislava, 2005)

[5] XLIII. Bratislavian Oncological Days (Bratislava, 2006)

iii. List of national journals published by the Organisation

none

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

[1] Autumn workshop: Genetic toxicology and cancer prevention (Bratislava, 2003)

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

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

[1] Altaner Č. Induction of Anti-Viral Immunity by Novel Bovine Leukemia Virus Structural Gene Vector. Bridges in Life Sciences, Budapest, Hungary 2003.

[2] Bartošová Z. Study proposal: HNPCC: SNP-LOH Study. International Society for Gastrointestinal Hereditary Tumours: The First Conference of InSIGHT. Newcastle, Great Britain, 2005.

[3] Gábelová A. Biological activity of binary mixtures. 28th Working Days of Czech and Slovak Society for Environmental Mutagens. Brno, Czech Republic, 2005.

[4] Altaner Č. Normal and cancer stem cells: Potential implication for cancer therapy. International Conference Cancer 2006: From molecular biology processes to tumor-tailored therapy. High Tatras, Slovakia, 2006.

[5] Bartošová Z. Advances in molecular diagnostics of hereditary non-polyposis colorectal cancer in Slovakia. International Conference Cancer 2006: From molecular biology processes to tumor-tailored therapy. High Tatras, Slovakia.

[6] Bies J. Leukemogenesis and c-myb: Story of a tightly regulated transcriptional regulator (prednáška). International Conference Cancer 2006: From molecular biology processes to tumor-tailored therapy. High Tatras, Slovakia, 2006.

[7] Bizik J. Nemosis - prospective cell based therapy. International Conference Cancer 2006: From molecular biology processes to tumor-tailored therapy. High Tatras, Slovakia, 2006.

[8] Chovanec M. Cellular response to oxidative DNA damage in Saccharomyces cerevisiae. International Conference Cancer 2006: From molecular biology processes to tumor-tailored therapy. High Tatras, Slovakia, 2006.

[9] Pirsel M. Repair of oxidative DNA damage in the helicase mutants (prednáška). International Conference Cancer 2006: From molecular biology processes to tumor-tailored therapy. High Tatras, Slovakia, 2006.

[10] Sedlák J. A possible role of dietary chemopreventive compounds in tumor therapy. International Conference Cancer 2006: From molecular biology processes to tumor-tailored therapy. High Tatras, Slovakia, 2006.

[11] Zajac V. FAP and HBOC: Two players in one playground. International Conference Cancer 2006: From molecular biology processes to tumor-tailored therapy. High Tatras, Slovakia, 2006.

[12] Marková E. Adverse effects of microwaves from GSM/UMTS mobile phones on human primary lymphocytes, fibroblast and stem cells. European Social Forum, Seminar on Mobile telephony and Public Health, Athens, Greece, 2006.

[13] Gábelová A. The influence of polymorphism in hOGG1 gene on the repair of oxidative DNA damage. 29th Working Days of Czech and Slovak Society for Environmental Mutagens. Brno, Czech Republic, 2006.

[14] Pleško, I. Collection and analysis of cancer mortality data in Slovakia. Plenary meeting of contributors to „Atlas of Cancer Mortality in Europe. France, 2006.

[15] Pleško, I. EUROCHIP project in Slovakia – problems and results. Workshop: EUROCHIP pilot studies. Amalfi, Italy, 2006.

[16] Pleško, I. First results of Pilot study – EUROCHIP project in Slovakia. Workshop EUROCHIP project“ – Milano, Italy, 2006.

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

[1] Altaner Č. President of International Conference Cancer 2006: From molecular biology processes to tumor-tailored therapy. High Tatras, Slovakia, 2006.

[2] Bartošová Z. Chair of Scientific and Local Organizing Committee of International Conference Cancer 2006: From molecular biology processes to tumor-tailored therapy. High Tatras, Slovakia, 2006.

[3] Bujalková M. Member of Scientific and Local Organizing Committee of International Conference Cancer 2006: From molecular biology processes to tumor-tailored therapy. High Tatras, Slovakia, 2006.

[4] Chudějová E. Member of Local Organizing Committee of International Conference Cancer 2006: From molecular biology processes to tumor-tailored therapy. High Tatras, Slovakia, 2006.

[5] Chalupa I. Autumn workshop: Genetic toxicology and cancer prevention. Bratislava 2004, 2005, 2006.

[6] Dudáš A. DNA Repair Workshop. Smolenice, Slovakia 2004.

[7] Dudášová Z. Member of Local Organizing Committee of International Conference Cancer 2006: From molecular biology processes to tumor-tailored therapy. High Tatras, Slovakia, 2006.

[8] Farkašová T. Autumn workshop: Genetic toxicology and cancer prevention. Bratislava 2004, 2005, 2006.

[9] Fridrichová I. Member of Local Organizing Committee of International Conference Cancer 2006: From molecular biology processes to tumor-tailored therapy. High Tatras, Slovakia, 2006.

[10] Gábelová A. Autumn workshop: Genetic toxicology and cancer prevention. Bratislava 2004, 2005, 2006.

[11] Gábelová A. VI. Comet Assay Workshop. Warsaw, Poland, 2005.

[12] Horváthová E. Autumn workshop: Genetic toxicology and cancer prevention. Bratislava 2004, 2005, 2006.

[13] Jakubíková J. Member of Local Organizing Committee of International Conference Cancer 2006: From molecular biology processes to tumor-tailored therapy. High Tatras, Slovakia, 2006.

[14] Kolarov J. Member of Organizing Committee of 2nd International Meeting on Yeast Apoptosis. Smolenice, Slovakia, 2003.

[15] Kleibl K. DNA Repair Workshop. Smolenice, Slovakia 2004.

[16] Krivulčík T. Member of Local Organizing Committee of International Conference Cancer 2006: From molecular biology processes to tumor-tailored therapy. High Tatras, Slovakia, 2006.

[17] Kováč M. Member of Local Organizing Committee of International Conference Cancer 2006: From molecular biology processes to tumor-tailored therapy. High Tatras, Slovakia, 2006.

[18] Lazarová M. Autumn workshop: Genetic toxicology and cancer prevention. Bratislava 2004, 2005, 2006.

[19] Lábaj J. Autumn workshop: Genetic toxicology and cancer prevention. Bratislava 2004, 2005.

[20] Piršel M. DNA Repair Workshop. Smolenice, Slovakia 2004.

[21] Slameňová D. Autumn workshop: Genetic toxicology and cancer prevention. Bratislava 2004, 2005, 2006.

[22] Šabová Ľ. Member of Organizing Committee of 2nd International Meeting on Yeast Apoptosis. Smolenice, Slovakia, 2003.

[23] Valovičová Z. Autumn workshop: Genetic toxicology and cancer prevention. Bratislava 2004, 2005, 2006.

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

[1] Altaner Č. Member of editorial board of Experimental Pathology and Parasitology (Bulgary)

[2] Altaner Č. Member of World Committee International Association for Comparative Research on Leukemia and Related Diseases“

[3] Altaner Č. Member of editorial board of Folia Biologica (Czech Republic)

[4] Altaner Č. Member of editorial board of Journal of Experimental and Clinical Cancer Research (Italy)

[5] Altaner Č. Member of editorial board of Nowotwory (Poland)

[6] Altaner Č. Member of editorial board of Viral Immunology (USA)

[7] Altaner Č. Member of Scientific Council of European School of Oncology (ESO)

[8] Altaner Č. National representative of Slovak Cancer Centre in Organization of European Cancer Institutes (OECI)

[9] Altaner Č. Member of Scientific Council of EU Program INTAS

[10] Altaner Č. Member of European Cancer Research Managers Forum (ECRM)

[11] Altaner Č. Member of Board of Experts of European Science Foundation (ESF)

[12] Babušíková O. Member of editorial board of Clinical Oncology (Czech Republic)

[13] Bizík J. Member of Executive Committee of European Association for Cancer Research (EACR)

[14] Gábelová A. Councillor of National branch in European Environmental Mutagen Society (EEMS)

[15] Gábelová A. Member of Committee of Czech and Slovak Society for Environmental Mutagenesis

[16] Novotný L. Dean of Faculty of Pharmacology, Kuwait University

[17] Novotný L. Head of Faculty of Pharmacology Council, Kuwait University

[18] Novotný L. Member of editorial board of Pharmacy Bulletin (Kuwait)

[19] Novotný L. Member of Kuwait University Council

[20] Novotný L. Honorary Member of Pharmaceutical Society of Egypt

[21] Pleško I. Honorary Member of International Association of Cancer Registries

[22] Pleško I. Member of Research Board of Advisors of the American Biographical Institute (USA)

[23] Pleško I. Auditor for population oncological registries evaluation in Europe (ENCR)

[24] Pleško I. Member of editorial board of Clinical Oncology (Czech Republic)

[25] Poláková K. Member of European Science Foundation Standing Committee European Medical Research Council (EMRC)

[26] Ujházy V. Member of editorial board of Clinical Oncology (Czech Republic)

v. List of international scientific awards and distinctions

[1] EC Marie Curie Actions Scholarship Award (Železníková T.)

[2] EEMS Travel Grant Award (Valovičová Z.)

[3] EEMS Young Scientists Travel Grant Award (Robichová S.)

[4] ESMO Best Exam Award (Mego M.)

[5] FEBS Travel Grant Award (Dudášová Z.)

[6] FEBS Travel Grant Award (Maršálková L.)

[7] Gordon Research Conferences Grant Award (Bartošová Z.)

[8] Christian Doppler Foundation Award (Lazarová M.)

[9] ICRETT Fellowship Award, UICC (Horváthová K.)

[10] ICRETT Fellowship Award, UICC (Gurský J.)
[11] ICRETT Fellowship Award, UICC (Horváthová E.)
[12] ICRETT Fellowship Award, UICC (Kimlíčková E.)
[13] ICRETT Fellowship Award, UICC (Lábaj J.)
[14] ICRETT Fellowship Award, UICC (Ovesná Z.)
[15] Marie Currie Fellowship Award (Jakubíková J.)
[16] Marie Currie Fellowship Award (Robichová-Gurská S.)
[17] Marie Currie Fellowship Award (Sokolíková B.)
[18] Marie Currie Fellowship Award (Sokolíková B.)
[19] Post-doctoral Fellowship Award Karolinska Institute, Sweden (Bačová G.)
[20] Post-doctoral Fellowship Award, University of Virginia, USA (Tomka M.)
[21] WHO Fellowship Award (Gábelová A.)
[22] WHO Fellowship Award (Lazarová M.)
[23] WHO Fellowship Award (Valovičová)

- **National position of the individual researchers**

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

[1] Altaner Č. Molecular biology of colorectal cancer. XLII. Bratislavian Oncological Days (Bratislava, 2005)
[2] Altaner Č. Nutrition and cancer. Conference on Nutrition and Food for 3rd Millennium – Nutrition and cancer (Nitra, 2006)
[3] Altaner Č. Scientific view on smoking maleficence. Konferencia: 31. Days of Health education of Ivan Stodola (Liptovský Ján, 2004)
[4] Altaner Č. The role of cancer stem cells in tumor development, prevention and targeted therapy. Conference on Nutrition and Food for 3rd Millennium – Nutrition and cancer (Nitra, 2006)
[5] Altaner Č. Cancer stem cells. XLII. Bratislavian Oncological Days (Bratislava, 2005)
[6] Bartošová Z. Molecular biology in diagnosis of v HNPCC. IX. Gastrophorum (Štrbské Pleso, 2004)
[7] Klobušická M: Options and limitations of cytochemistry in diagnosis of leukemia. a limitacie cytochemie v diagnostike leukemii. Lojd's Histochemical Day (Bratislava, 2004)

[8] Pleško, I. Trends in the epidemiology of breast cancer in Slovak Republic. XL. Bratislavian Oncological Days (Bratislava, 2003)

[9] Zajac V. Molecular-genetic approaches to colorectal cancer analyses. IX. Gastrophorum (Štrbské Pleso, 2004)

[10] Zavodna K., Krivulčík T., Bartošová Z. New genetic aspects of stomach cancers. X. Gastrophorum (Štrbské Pleso, 2006)

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

[1] Altaner Č. Member of Organising and Programme Committee of XL. Bratislavian Oncological Days (Bratislava, 2003)

[2] Babušíková O. Member of Organising and Programme Committee of XL. Bratislavian Oncological Days (Bratislava, 2003)

[3] Sedlák J. Member of Organising and Programme Committee of XL. Bratislavian Oncological Days (Bratislava, 2003)

[4] Gábelová A. Member of Organising and Programme Committee of Autumn workshop: Genetic toxicology and cancer prevention (Bratislava, 2003)

[5] Horváthová E. Member of Organising and Programme Committee of Autumn workshop: Genetic toxicology and cancer prevention (Bratislava, 2003)

[6] Chalupa I. Member of Organising and Programme Committee of Autumn workshop: Genetic toxicology and cancer prevention (Bratislava, 2003)

[7] Robichová S. Member of Organising and Programme Committee of Autumn workshop: Genetic toxicology and cancer prevention (Bratislava, 2003)

[8] Slameňová D. Member of Organising and Programme Committee of Autumn workshop: Genetic toxicology and cancer prevention (Bratislava, 2003)

[9] Altaner Č. Member of Organising and Programme Committee of XLI. Bratislavian Oncological Days (Bratislava, 2004)

[10] Babušíková O. Member of Organising and Programme Committee of XLI. Bratislavian Oncological Days (Bratislava, 2004)

[11] Sedlák J. Member of Organising and Programme Committee of XLI. Bratislavian Oncological Days (Bratislava, 2004)

[12] Altaner Č. Member of Organising and Programme Committee of XLII. Bratislavian Oncological Days (Bratislava, 2005)

[13] Babušíková O. Member of Organising and Programme Committee of XLII. Bratislavian Oncological Days (Bratislava, 2005)

[14] Sedlák J. Member of Organising and Programme Committee of XLII. Bratislavian Oncological Days (Bratislava, 2005)

[15] Altaner Č. Member of Organising and Programme Committee of XLIII. Bratislavian Oncological Days (Bratislava, 2006)

[16] Babušíková O. Member of Organising and Programme Committee of XLIII. Bratislavian Oncological Days (Bratislava, 2006)

[17] Sedlák J. Member of Organising and Programme Committee of XLIII. Bratislavian Oncological Days (Bratislava, 2006)

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

[1] Ujházy V. Chief-Editor of international CC journal Neoplasma published in Slovakia

[2] Klobušická M. President of Slovak Cancer Research Foundation

[3] Bizík J. Vice-president of Slovak Cancer Research Foundation

[4] Altaner Č. Member of Scientific Board of Slovak League Against Cancer

[5] Ujházy Č. Member of Scientific Board of Slovak League Against Cancer

[6] Altaner Č. Member of editorial board of Neoplasma

[7] Chorváth B. Member of editorial board of Neoplasma (till 2003)

[8] Cuninková M. Member of editorial board of Urology

[9] Kolarov J. Member of Scientific board of Faculty of Natural Sciences of Comenius University, Bratislava

[10] Tóthová-Romanová. Member of Senatus Academicus of Faculty of Natural Sciences UCM Trnava

[11] Brozmanová J. Member of PhD Defense Committee In Genetics

[12] Piršel M. Member of PhD Defense Committee In Genetics

[13] Slameňová D. Member of PhD Defense Committee In Genetics

[14] Gábelová A. Member of PhD Defense Committee In Genetics

[15] Luciaková K. Member of PhD Defense Committee In Genetics

[16] Kolarov J. Member of PhD Defense Committee In Biochemistry

[17] Altaner Č. Member of PhD Defense Committee In Virology

[18] Altaner Č. Member of PhD Defense Committee In Oncology

[19] Babušíková O. Member of PhD Defense Committee In Oncology

[20] Bies J. Member of PhD Defense Committee In Oncology

[21] Bizík J. Member of PhD Defense Committee In Oncology

[22] Pleško I. Member of PhD Defense Committee In Oncology

[23] Piršel M. Member of PhD Defense Committee In Oncology

[24] Sedlák J. Member of PhD Defense Committee In Oncology

[25] Slameňová D. Member of PhD Defense Committee In Oncology

[26] Ujházy V. Member of PhD Defense Committee In Oncology

[27] Babušíková O. Member of PhD Defense Committee In Immunology

[28] Pleško I. Member of PhD Defense Committee In Epidemiology

[29] Kolarov J. Member of DSc Defense Committee In Biochemistry

[30] Babušíková O. Member of DSc Defense Committee In General Biology

[31] Babušíková O. Member of DSc Defense Committee In Antropology

[32] Altaner Č. Member of DSc Defense Committee In Genetics

[33] Brozmanová J. Member of DSc Defense Committee In Genetics

[34] Altaner Č. Member of DSc Defense Committee In Virology

[35] Altaner Č. Member of DSc Defense Committee In Oncology

[36] Babušíková O. Head of DSc. Defense Committee In Oncology

[37] Ujházy V. Member of DSc. Defense Committee In Oncology

[38] Pleško I. Member of DSc Defense Committee In Epidemiology

[39] Pleško I. Member of DSc Defense Committee In Hygiene

[40] Altaner Č. Member of State Programme and Research & Development Sub-Programme Council “Genomics of cancer, heart and infection diseases for healthier human and animal population”

[41] Altaner Č. Member of Scientific College of Slovak Academy of Sciences for Molecular Biology

[42] Babušíková O. Member of Scientific College of Slovak Academy of Sciences for Medical Sciences

[43] Ujházy V. Member of Scientific College of Slovak Academy of Sciences for Medical Sciences

[44] Hlubinová K. Committee Member of Section for Research Workers with Tissue Cultures

[45] Chalupa I. Head of Committee of Section for Research Workers with Tissue Cultures

[46] Klobušická M. Member of Committee of Slovak Histology Society at SAS

[47] Babušíková O. Member of Slovak Research Grant Agency VEGA Commission for pharmacological sciences

[48] Piršel M. Member and from 2005 Vice Head of Slovak Research Grant Agency VEGA Commission for molecular and cellular biology

[49] Piršel M. Member of Headquarters of Slovak Research Grant Agency VEGA

iv. List of national awards and distinctions

[1] The Institute received a Medal „FACULTAS RERUM NATURALIUM CONDITA MCMXL UNIVERSITAS COMENIANA BRATISLAVENSIS“ from the dean of Comenius University

[2] Altaner Č. was awarded the „Slovak Academy of Sciences Personality“

[3] Brozmanová J. was awarded the „Slovak Academy of Sciences Personality“

[4] Altaner Č. was awarded the „Gold Medal of Slovak Medical Society“

[5] Altaner Č. was awarded the „Silver Medal of Comenius University“

[6] Chalupa I. was awarded the „Silver Medal of Slovak Medical Society“

[7] Altaner Č. was awarded the “Orin-Panacea”

[8] Pleško I. was awarded the “Orin-Panacea”

[9] Altaner Č. was awarded the “Premium Award For Scientific Literature 2003”

[10] Bartošová Z. was awarded in 2003 the „Scientist Of The Year 2002“

[11] Chovanec M. was awarded in 2003 the „Young Scientist Of The Year 2002“

[12] Jakubíková J. was awarded in 2006 the „Young Scientist Of The Year 2005“

[13] Poláková K. received a “Honourable mention in Scientist of the Year 2003“

[14] Baušíková O. received a “Honourable mention in Scientist of the Year 2005“

[15] Bizík J. received a “Honourable mention in Scientist of the Year 2005“

[16] Slameňová D. received a “Honourable mention in Scientist of the Year 2005“

[17] Slameňová D. - 2. nd place in „Environment Preservation Techniques 2003“

[18] Lábaj J. recieved „A Progressive Idea“ Award by Ministry of Environm. of SR

[19] Group of D. Slameňová received „The SAS Price for Internat. Collaboration“

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

One scientific product we are proud of is the population-based National Cancer Registry covering the incidence of cancer in whole of Slovakia. The data from this data base is the basis for modulation of health policy not only in Slovakia but also in the European Union as well.

Our Institute initiated and established molecular-genetic testing of hereditary forms of several cancer syndromes in Slovakia. This achievement positively influenced the clinical management of patients with hereditary predisposition to breast and ovarian cancer, two types of colorectal carcinomas, and medullary thyroid carcinoma. In addition by testing of family members we identified asymptomatic mutation carriers being enrolled in preventive screening and non-carriers released from psychological stress.

The Institute established for the first time flow cytometry analysis for immunophenotyping of leukemia and lymphoma in Slovakia.

The international status is expressed also in the ability to edit the international journal NEOPLASMA with permanently increasing impact factor.

4. Project structure, research grants and other funding resources

- **International projects and funding**

i. List of major projects within the European Research Area – 5th and 6th 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, funding, responsible person in the Organisation and his/her status in the project, e.g. coordinator, principal investigator, investigator)

[1] 5th FP EU project: Novel approaches towards the diagnosis and therapy of tumours with microsatellite instability. Grant No. QLG1-CT-2000-01230 (in EU) or ISVVP 51-98-9241-00/2000 (in SAS), Duration: 10/2000-3/2004, Funding from EC: 110 000 € and SAS: 3,801.000 SKK, Principal investigator in CRI SAS: Zdena Bartošová

[2] 5th FP project: Effects of polycyclic aromatic hydrocarbons (PAHs) in environmental pollution on exogenous and endogenous DNA damage. Grant No. QLRT 2000-00091 (in EU) or ISVVP 51-98-9292-00/2001 (in SAS), Duration: 01/2001-03/2004, Funding from EC: 23 800 € and SAS: 271 400 SKK, Principal investigator in CRI SAS: Alena Gábelová

[3] 6th FP project: Application-oriented studies on regulatory networks involved in lipid homeostasis and atherosclerosis. Grant No. LSHM-CT-2006-037498, Duration: 10/2006 – 09/2009, Funding from EC: 201 954 € expected, Principal investigator in CRI SAS: Peter Baráth

[4] 6th FP project: EUROCHIP-II - European Cancer Health Indicator Project Phase II. Grant No. OJ 2003/C62/04, Duration: 01/2006 – 12/2008, Funding from EC: 17 800 € expected, Principal investigator in CRI SAS: Ivan Pleško

ii. List of other international projects incl. funding

[1] FIRCA grant: Development of retrovirus prototype DNA vaccine for prevention of infections with more complex retroviruses. Grant No. 1 R03 TW01217-01, Duration 01/2000 – 12/2004, Funding: 27 000 USD, Principal investigator in CRI SAS: Čestmír Altaner

[2] Slovak – USA intergovernmental agreement project: Structure-function analysis of the XPB/ERCC3 transcription-repair tumor-suppressor protein. Grant No. 031/2001, Duration: 07/2002 – 06/2005, Funding: 931 000 Sk, Principal investigator in CRI SAS: Miroslav Piršel

[3] Slovak – Denmark project: Influence of bone marrow transplantation on the life span of ageing mice. Duration: 01/2006-12/2008, Funding: 617 849,- Sk from Denmark, Principal investigator in CRI SAS: Veronika Altanerová

[4] Slovak – Austria intergovernmental agreement project: In vitro and in vivo studies of antimutagenic properties of glucans. Grant No. SAIA 39s4, Duration: 01/2003 – 12/2005, Funding: 218 862 Sk from Slovakia and 2382 € from Austria, Principal investigator in CRI SAS: Darina Slameňová

[5] Slovak – Czech intergovernmental agreement project: Platinum complexes: From DNA damage to cancer chemotherapy. Grant No. 143, Duration 01-2004-12/2005, Funding: 56 000 Sk, Principal investigator in CRI SAS: Miroslav Piršel

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

[1] Slovak – Italy intergovernmental agreement project: Rational design, structure determination and activity testing of anticancer and antimicrobial peptides. Grant No. SAV-CNR 9/06/Bt/00, Principal investigator in CRI SAS: Vladimír Frecer

[2] Multilateral European project: GLOBOCAN - Cancer Incidence and Mortality Worldwide. IARC Cancerbase. Duration: Long-term from 1995, Principal investigator in CRI SAS: Ivan Pleško

[3] Multilateral European project: Cancer Incidence in Five Continents. Duration: Long-term from 1973, Principal investigator in CRI SAS: Ivan Pleško

[4] Multilateral European project: Atlas of Cancer Mortality in Europe. Duration: 2003 – 2005, Principal investigator in CRI SAS: Ivan Pleško

[5] Multilateral European project: EUROTIS-European Incidence Thyroid Cancer Study. Duration: 2004 – 2005. Principal investigator in CRI SAS: Ivan Pleško

[6] Multilateral European project: EUROCHIP – II, Health Indicators – Monitoring Cancer in Europe – II. Duration: 2003 - , Principal investigator in CRI SAS: Ivan Pleško

[7] Multilateral European project: ACCIS Programme - Automated Childhood Cancer Information System. Duration: Long-term from 2000, Principal investigator in CRI SAS: Ivan Pleško

[8] Multilateral European project: EUROCIM - European Cancer Incidence and Mortality Database. Duration: Long-term from 1995, Principal investigator in CRI SAS: Ivan Pleško

[9] Multilateral European project: EUROCARE-3 study - Understanding the reasons for cancer patients´ survival differences in Europe. Grant No. ERB IC-CT98-0205, Duration: 2003-Long-term, Principal investigator in CRI SAS: Ivan Pleško

[10] Collaboration with: Institute of Food Research, Norwich, UK

[11] Collaboration with: Instituto di Strutturistica Chimica “Giordano Giacomello”, C.N.R. – Sezione di Trieste, Trieste, Italy

[12] Collaboration with: Clinical Institute of Medicinal and Chemical Laboratory Diagnostics, General Hospital of Vienna, Vienna University Austria

[13] Collaboration with: Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Kuwait University, Kuwait

[14] Collaboration with: Lawrence Livermore National Laboratory, Livermore, USA

[15] Collaboration with: NIEHS, NIH, Research Triangle Park, Chapel Hill, NC USA

[16] Collaboration with: Paterson Institute for Cancer Research, Section of Genome Damage and Repair, Manchester, United Kingdom

[17] Collaboration with: Genome Damage and Stability Centre, University of Sussex, Brighton, UK

[18] Collaboration with: Institute of Microbiology and Genetics, University of Vienna, Austria

[19] Collaboration with: Dermatology Unit, University of Victor Segalen, Bordeaux, France

[20] Collaboration with: Department of Virology, University of Helsinki, Finland

[21] Collaboration with: Equipe Information et Programmation Cellulaire, Universite de Rennes I, France

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

[23] Collaboration with: University of Salzburg, Institute of Genetics and General Biology, Salzburg, Austria

[24] Collaboration with: Laboratory of Histology-Embryology, Faculty of Medicine Aristotle University of Thessaloniki, Greece

[25] Collaboration with: Cancer Biomarkers and preventive group, Biocentre, University of Leicester, UK

[26] Collaboration with: Folkehelsa, National Institute of Public Health, Oslo, Norway

[27] Collaboration with: Department of Biosciences, University of Helsinki, Helsinki, Finland

[28] Collaboration with: Radiation Genetics and Chemical Mutagenesis Leiden University Medical Center Leiden, Holandsko

[29] Collaboration with: Laboratory for Stem Cell Research, Aalbory University, Aarhus, Denmark

[30] Collaboration with: Institute of Molecular Cancer Research, Zürich, Switzerland

[31] Collaboration with: Institute of Inorganic Chemistry, University of Vienna, Austria,

[32] Collaboration with: Institute of Organic Chemistry, University of Tubingen, Germany

[33] Collaboration with: Department of Genetic, Toxicology and Microbiology, Stockholm University Stockholm, Sweden

[34] Collaboration with: Cancer Research UK Laboratories, Weatherall Institute of Molecular Medicine, University of Oxford, John Radcliffe Hospital, Oxford, UK

[35] Collaboration with: University of Szeged, First Department of Medicine, Szeged, Hungary

[36] Collaboration with: Laboratory of Cellular Oncology, National Cancer Institute, Bethesda, USA

- **National projects and funding**

i. List of projects supported by the Agency for the Promotion of Research and Development (APVV/APVT), National Research Programmes, and their funding

[1] Epithelial-mesenchymal transition in the model of breast carcinoma stem cells in vitro. Principal investigator in CRI SAS: Sedlák J., 3/2006-2/2009, APVV-51-017505, Funding in 2006: 1 286 000,- SKK

[2] Further in vivo characterization of the mutant and polymorphic DNA ligase IV proteins found in LIG4 patients. Principal investigator in CRI SAS: Chovanec M., 5/2006 – 4/2009, APVV-51-042705, Funding: 1 007 000,- SKK in 2006

[3] The role of mitochondria in the life and death of a cell. Principal investigator in CRI SAS: Luciaková K., 1/2003-12/2005, APVT-26-002102, Funding: 2 513 000,- SKK

[4] Role of hamster ERCC3/XPB tumor-suppressor protein in the repair of oxidative DNA damage. Principal investigator in CRI SAS: Piršel M., 9/2002 – 9/2005, APVT-51-003202, Funding: 1 699 000,- SKK

[5] The Role Intraepithelial Bacteria in Processes of Colorectal Carcinogenesis. Principal investigator in CRI SAS: Zajac V., 1/2002 - 12/2005, APVT-51-010802, Funding: 2 394 000,- SKK

[6] Role of polymorphisms of DNA repair genes hOGG1 and XPD on DNA damage processing in human cell lines. Principal investigator in CRI SAS: Gurská S., 1/2005 - 12/2007, APVT-51-015304, Funding: 1 396 000,- SKK

[7] New environmental friendly use of lignin biopolymers from wastes of chemical wood treatment for chemoprevention of cancer and genetic diseases. Co-Principal investigator in CRI SAS: Slameňová D., 1/2004 – 12/2006, APVT-51-032602, Funding: 830 000,- SKK

[8] Plant extracts - anti-inflammatory, cytotoxic ans antimutagenic effects in animals. Co-Principal investigator in CRI SAS: Slameňová D., 01/2005 - 12/2007, 51-015404, Funding: 430 000,- SKK

ii. 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	2003	2004	2005	2006
number	16	20	24	22
funding (millions of SKK)	1.834	2.397	2.475	3.030

- **Summary of funding from external resources**

External resources	2003	2004	2005	2006	total	average
external resources (millions of SKK)	15.124	20.021	24.845	10.659	70.649	17.662
external resources transfered to coooperating research organisations (millions of SKK)	0.000	0.000	0.000	0.000	0.000	0.000
ratio between external resources and total salary budget	0.771	1.002	1.186	0.489	3.448	0.862
overall expenditures (millions of SKK)	51.699	56.701	65.635	50.436	224.471	56.118

Supplementary information and/or comments on research projects and funding resources

Important external resources come from Slovak Cancer Research Foundation which co-financed important new equipment such as DNA sequencer, Wave System, LCMD Device. In addition, it supports young scientists by travel grants for participation on international conferences. Slovak League Against Cancer supported purchase of scientific journals, stem cell research and epigenetic studies.

For majority of the Grants funded by Scientific Grant Agency of the Slovak Academy of Sciences and the Ministry of Education (VEGA) hold that the goals are achieved with the help of international collaborations since the funding is insufficient (average funding per year per project: ~ 3000 €).

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)

Genetics 15-03-9
Oncology 15-14-9
Genetics 4.2.4.
Oncology 7.1.15

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	31.12.2003			31.12.2004			31.12.2005			31.12.2006		
number of potential PhD supervisors	33			34			34			37		
PhD students	number	defended thesis	students quitted	number	defended thesis	students quitted	number	defended thesis	students quitted	number	defended thesis	students quitted
internal	19	5	1	16	2	7	13	2	6	10	7	5
external	5	0	0	4	2	0	4	0	0	1	4	0
supervised at external institution by the research employees of the assessed organisation	0	0	0	0	0	0	0	0	0	0	0	0

iii. Postdoctoral positions supported by

a) external funding (specify the source)

Nine students have been supported by European Social Fund Project to continue in PhD studies in order to allow them to defend their thesis

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

1 postdoc position

iv. Summary table on pedagogical activities in undergraduate programmes for each year

Teaching	2003	2004	2005	2006
lectures (hours/year)	192	85	52	57
practicum courses (hours/year)	5250	5702	4953	8068
supervised diploma works (in total)	21	24	21	15
members in PhD committees (in total)	5	8	5	6
members in DrSc. committees (in total)	3	4	1	4
members in university/faculty councils (in total)	2	3	1	2
members in habilitation/inauguration committees (in total)	1	2	0	1

v. List of published university textbooks

N/A

vi. Number of published academic course books

N/A

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

N/A

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

Internal practice of the institute for PhD is based on 3 CC papers. Three years for PhD study are usually not sufficient to achieve this standard. Thus, students assigned as quitted (in the table) include also students continuing in their PhD study after expiration of regular 3 years. The institute's policy is to give additional time to these students to stay at the institute and finish their PhD studies with the defence. The changes in law in 2006 allow 4 years for PhD study.

Although the institute members have not published any university textbook or academic course books, some of them participated on such activities writing specific chapters in them. The monograph "Onkologia" is the recommended textbook for medical students.

There are not official joint research laboratories/facilities with the Universities; however, the unofficial collaboration is extensive including joint papers.

6. Direct output to the society (applications of results, popularisation and outreach activities)

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

[1] results showing that leukemia/associated phenotypes in acute leukemia are not only those with lineage infidelity markers coexpression, but also those with a tendency to drop specific normal markers for the given lineage – result applied for correct assessment of minimal residual disease in leukemia patients (Babušíková O.)

[2] finding that CD58 marker may help to discriminate between leukemia B-lymphoblasts and healthy regenerating B-cells (Babušíková O.)

[3] establishment of methods estimating the number of stem cells after growth factors stimulations - important data before decision for autologous transplantation (Babušíková O.)

[4] results achieved in molecular-genetic studies of patients with familial adenomatosis coli (FAP) were applied in clinical institutions for clinical management of FAP families (Zajac V.)

[5] results achieved in molecular-genetic studies of patients with Hereditary non-polyposis colorectal cancer (HNPCC) were applied in clinical institutions for clinical management of HNPCC families (Bartošová Z. and Fridrichová I.)

[6] results achieved in molecular-genetic studies of patients with hereditary breast and ovarian cancer (HBOC) were applied in clinical institutions for clinical management of families HBOC families (Zajac V.)

[7] results achieved in molecular-genetic studies of patients with multiple endocrine neoplasia (MEN-2 syndrome) were applied in clinical institutions for clinical management of families affected families with this syndrome (Altanerová V.)

[8] methodological protocol for use in clinic for detection of multiple endocrine neoplasia (Altanerová V.)

[9] methodological protocols for use in clinic for screening of germline mutations in the genes responsible for genetic predisposition to breast and ovarian cancer (*BRCA1, BRCA2, CHEK2*) (Čierniková S.)

[10] methodological protocols for use in clinic for identification of germline mutations in *APC* gene in familial adenomatosis coli (FAP). (Zajac V.)

[11] methodological protocols for use in clinic for screening of germline mutations in *MLH1*, *MSH2* and *MSH6* genes in HNPCC suspected patients (Závodná K.)

[12] methodological protocol for use in clinic for standardised nomenclature of HNPCC germline mutations (Bujalková M.)

[13] methodological protocol for evaluation of methylation in proximal region of *MLH1* gene using genomic sequencing of bisulfide modified DNA (Fridrichová I. and Alemayehu A.)

[14] methodological protocol for evaluation of microsatellite instability and loss of heterozygosity by MSI markers DNA (Fridrichová I. and Alemayehu A.)

[15] methodological protocol for isolation of lymphocytes from human peripheral blood. Conditions for freezing and defrosting (Gábelová A.)

[16] methodological protocol adapted for use in clinic for alkali single cell gell electrophoresis and detection of oxidative damage (Gábelová A.)

[17] methodological protocol for detection of polymorphisms in DNA repair genes (Gábelová A.)

[18] methodological protocols for use in clinic for refinement of human leukaemia and lymphoma diagnosis using flow cytometry (Babušíková O.)

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

[1] Data for National Oncology Registry, Ministry of Health of Slovak Republic

[2] Expertise for Governmental Research & Development Programme

[3] Data for state health institutes

[4] Data for Slovak Oncology Society

[5] Data for WHO

[6] Data for UICC

[7] Data for IARC

iii. List of the most important popularisation activities

[1] Doors Open Days

[2] Organization or participation on Press conferences

[3] Participation on public exhibitions

[4] Lectures for students and teachers of high schools

[5] Articles in press media and internet

[6] Appearances in telecommunication media

iv. List of patents issued abroad, incl. revenues

N/A

v. List of the patents issued in Slovakia, incl. revenues

N/A

vi. List of licences sold abroad, incl. revenues

N/A

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

N/A

viii. List of contracts with industrial partners, incl. revenues

[1] Contract with Daiwa Pharmaceutical, Japan

[2] Contract with AllDeco, Ltd. Slovakia

ix. List of research projects with industrial partners, incl. revenues

[1] Monitoring of immunological parameters of multiple myeloma patients during course of Biobran consumption. Duration: 01/2005-12/2006, Funding: Daiwa Pharmaceutical, Japan: 1 295 358 Sk, Principal investigator in CRI SAS: Ján Sedlák

[2] Particular response markers in men occupationally exposed to radiation: cellular damage response and apoptosis. Project Consumer: AllDeco Ltd., Duration: 07/2002-12/2003, Project No. 51-519043-00/2002, Funding: 350 000,- Sk, Principal investigator in CRI SAS: Ján Sedlák

x. Summary of outreach activities

Outreach activities	2003	2004	2005	2006	total
studies for the decision sphere, government and NGOs, international and foreign organisations	5	5	4	3	17
articles in press media/internet popularising results of science, in particular those achieved by the Organization	6	10	1	18	35
appearances in telecommunication media popularising results of science, in particular those achieved by the Organization	13	8	13	36	70
public popularisation lectures	0	0	22	10	32

xi. Supplementary information and/or comments on applications and popularisation activities

The members of the institute often participated on the press conferences mainly organized by Slovak Cancer Research Foundation or League Against Cancer (altogether participation on 15 press conferences within 2003-2006). The results on genetic predisposition to colorectal cancer were presented to public in 2003 as a part of exhibition “Science for the people” in Slovak National Museum and in 2004 as a part of exhibition “Science for the people” in Bratislava Castle. The institute was organizing Doors Open Day for public, particularly students of high schools in years 2004 and 2006. Several hundreds of students visited the institute during these events. In 2005, the institute organized popularising lectures from oncology for students of high schools and Workshop for teachers teaching “Oncology Education” at high schools. In addition to 18 popularising articles in press media/internet in 2006, the 79 short messages related to the institute or its members appeared in these sources.

7. Background and management. Staffing policy and implementation of findings from previous assessments

According to previous assessment the institute was classified as “A” - the Organisation with excellent results.

i. Summary table of personnel

Personnel	2003	2004	2005	2006
all personel	108	110	115	129
research employees from Tab. Research staff	48	50	50	59
FTE from Tab. Research staff	37.5	37.5	37	46.25
averaged age of research employees with university degree	49.5	46.4	44.8	41.1

ii. Professional qualification structure

Number of	2003	2004	2005	2006
DrSc.	12	11	10	10
PhD / CSc.	38	39	41	49
Prof.	2	2	1	1
Doc./Assoc. Prof.	2	3	2	2

iii. 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: Laser Capture Micro-dissection (LCMD) System PALM MicroBeam, Coulter Epics Altra Flow Cytometer, ABI PRISM 310 Genetic Analyzer, Fluorimeter PolarStar Optima and LUMIstar, Wave DHPLC System, Rotor Gene 2000 Real-Time Cycler, Electron microscope. The institute has facilities for work with mutagens, GMO and radioactivity and possess modern animal facility. In addition to computer equipment for every researcher, the institute has intranet information system Forum and grant information system G.I.S.

It is of urgent need to create tumour bank in Slovakia. Our institute has ambition to participate on establishment of this crucial facility for further progress in cancer research or at least to serve as an advisor and consumer of the samples. The effective use of LCMD device at the institute requires establishment of modern histopathological laboratory with laminary box, microtome, cryostate, staining automatic device and a digital archive. The Genetic Analyzer ABI PRISM 310 with single capillary which is currently in use has low capacity and higher-throughput analyzer such as 48-plex with 48 capillaries would be desirable. For establishment of proteomics at the institute MALDI TOF is required. To house new equipment and build new laboratories 1-2 floors need to be build-up to current building.

iv. Status and development of bibliographic resources, activities of the Organisation's library and/or information centre

The institute possess library with 5425 library units (books, journals, monographs, PhD thesis, etc.). It offers loans of periodicals and monographs for members of institute, inter-libraries copies of articles and loans of monographs. The library owns periodical journals (in 2003: 12, in 2004: 19, in 2005: 20, in 2006: 20). Some bibliographic units maybe studied only in the library.

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

There were no substantial suggestions to our research activity in previous assessment in 2003.

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

Infrastructure:

The Institute is located in the building, which was constructed very poorly. The thermo insulation is insufficient, windows are of very bad quality, and therefore we have problems in the winter to heat enough some part of the building. Especially the library is not usable during the winter. Some parts of building coat are falling down.

Personnel development

The personal development is primarily focused on young scientist. The institute is carrying out educational project “Innovative education programme of young creative experts in cancer research” funded partially by European Social Fund. The project is primarily supporting PhD students to finish high quality PhD thesis extending regular PhD study period. The next objectives of the project are: to improve the general as well as specialised knowledge related to cancer by attending the Courses of Molecular Oncology in native and English language, to increase communication skills and capability to actively participate in scientific discussions, to learn new techniques from all laboratories at the institute, to learn popularising the scientific work to public. The project is also financially supporting participation at the national and international conferences. Overall, project is designed to bring-up exceptional young creative scientists in cancer research area.

Other information relevant to the assessment

Every third citizen of Slovakia, as well as citizen of the European Union in his/her life is faced with cancer reality. From this reason, in many countries the cancer management and research belongs to the highest priority of the society. We feel that it is not the case in Slovakia. In our opinion, it is harm to many people, because the modern molecular oncology brings new possibilities in cancer management, which could improve the cancer patient survival.