ACADEMY OF SCIENCES OF THE CZECH REPUBLIC

INSTITUTE OF BIOPHYSICS

RESEARCH REPORT

2003

Brno 2004

CONTENTS

I. INTRODUCTION

Research activities of the Institute of Biophysics AS CR were concentrated on the continuation of the long-term task, the running Institutional Research Plan (IRP), similarly as in the year 2003. These activities led to a number of new significant results shown in chapter II, and quoted in the list of papers in the chapter III of this Report.

Successful research activities contributed to the establishment of research contacts with scientific institutions in the CR and abroad (chapter IV). The fruitful cooperation has been developed with universities: researchers of the IBP were widely integrated in education programs, as reported in the chapter V.

Last but not least, organizational activities that helped to establish optimal conditions for the scientific work should be mentioned as well:

- elaboration of documents required for evaluation of research achievements obtained in the years 1999 – 2003,

  in accordance with the law No. 130/2002 Coll., concerning the support of the research and development from the budget of the CR, and in accordance with the regulation rule of the government of the CR No. 462/2002 Coll., the Academic Council of the AS CR proclaimed rules for the evaluation of institutes of the AS CR. In this respect there were elaborated requested materials.

- specification of the Conception of research activities of the IBP for the years 2005 – 2010

  the specification of conceptions of all Laboratories of the Institute allowed to elaborate the proposal of the new IRP, "*The Biophysics of Dynamic Structures and Functions of Biological Systems*", intended for five years since the year 2005.

- categorization of researchers to salary classes

  in the compliance with results of the evaluation by attestation commissions of members of the Institute staff in 2002, all researchers were classified into five qualification classes by the 1st April, 2003. At the end of 2003 they were categorized into 16 salary classes; this categorization will be valid from the 1st January, 2004.

- further extension of work-, spaces, mainly laboratories

    towards the end of 2003 total reconstruction of the former greenhouse in the area of the Institute has been completed. The new laboratory workplace is allocated to the Laboratory of Plant Development genetics.

In 2003 new Scientific Council of the Institute has been elected and consists of the following members: *S. Kozubek* (chairman), *J. Hofmanová* (vice-chairman), *J. Fajkus, A. Lojek, J. Šponer, B. Vyskot*, - internal members; M. Gellnar (Fac. of Sci, MU), B. Vojtěšek (Masaryk Oncol. Inst.), J. Žaloudík (Med. Fac., MU) - external members.

There is already a tradition to popularize research activities in the frame of the program "Open Door Days". In the year 2003, 125 visitors came to see facilities of the IBP and demonstrations of unique scientific devices.

The scientific activities of researchers were appreciated and awarded:

B. Vyskot has been elected the regular member of the Learned Society of the CR
E. Paleček vas appointed the "trustee" of the board of "The Mendel Trust"
K. Kozubík and *J. Hofmanová* were awarded the golden medal of the Faculty of Sci, UPJŠ in Košice, the SR, - for their long-term collaboration with the Faculty and significant contribution to its development and forming the Scientific profile.
S. Kozubek was appointed a honorary member of The Society for Radiobiology and Emergency Planning
J. Fojta and *J. Šponer* obtained "the Bonus of Otto Wichterle for Young Researchers of the AS CR"
J. Kašpárková was given the Prize of the Ministry of Health of the CR in the category "Young research worker"
J. Hofmanová and *A. Kozubík* were given the Prize of the University of Health of the CR as co-investigators in the grant project NC/6171-3
S. Hasoň, M. Lengerová, E. Sýkorová were awarded the prize of the Institute of Biophysics.

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II. SCIENTIFIC ACTIVITIES

Individual Laboratories are grouped into five Programs:

I. Biophysical Chemistry of Macromolecules

Laboratory of Biophysical Chemistry and Molecular Oncology - LBCMO
Prof. RNDr. Emil Paleček, DrSc.

Laboratory of Physics of Biomacromolecules - LBP
Prof. RNDr. Vladimír Vetterl, DrSc.

Laboratory of Structure and Dynamics of Nucleic Acids - LSDNA
doc. RNDr. Jiří Šponer, DrSc.

II. Biophysics of Nucleic Acid Complexes

Laboratory of Molecular Biophysics and Pharmacology - LMBP
Prof. RNDr. Viktor Brabec, DrSc.

Laboratory of DNA Molecular Complexes - LDMC
RNDr. Jiří Fajkus, CSc.

Laboratory of Analysis of Chromosomal Proteins - LACP
RNDr. Michal Štros, CSc.

III. Biophysics and Bioinformatics of Genomes

Laboratory of CD Spectroscopy of Nucleic Acids - LSNA
doc. RNDr. Michaela Vorlíčková, DrSc.

Laboratory of DNA Biophysics and Bioinformatics of Genomes - LDBGB
RNDr. Jaroslav Kypr, CSc.

Laboratory of Molecular Epigenetics - LME
RNDr. Aleš Kovařík, CS

IV. Molecular Cytology and Cytogenetics

Laboratory of Molecular Cytology and Cytometry - LMCC
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Laboratory of Plant Development Genetics - LPDG
Prof. RNDr. Boris Vyskot, DrSc.

Laboratory of Plant Development Molecular Analysis - LMAPD
RNDr. Břetislav Brzobohatý, CSc.

V. Kinetics of Cell Populations

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Laboratory of Pathophysiology of Free Radicals - LFRP
RNDr. Antonín Lojek, CSc.

Laboratory of Experimental Hematology - LEH
MUDr. Michal Hofer, CSc.

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Laboratory of Computers and Information Systems - LCIS

RNDr. Josef Jursa, CSc.

RESEARCH PROJECTS WERE SUPPORTED BY GRANTS:

From the Institutional Research Plan Z5004920 „Biophysical Properties of Living Systems and their Changes under the Influence of Environmental Factors“

In addition, IBP participated in two research plans of Universities in co-operation with Masaryk University, Faculty of Sciences and Informatics

From Grant Agency of the Academy of Sciences, CR*:*

- 12 standard grants, 3 junior grants
- Program „The Support of the Targeted Research and Development“, 3 grants
- Project „Development of Basic Science Research in the Key Areas of Science“, 3 grants
- Program „The Advancement in Research Equipment in Progressive Fields of Science“, 1 grant

From Grant Agency of the Czech Republic

- 26 individual grants, in 24 of these scientists of IBP were as principal investigators, in two grants as partial investigators
- 10 postgraduate grants

From Grant Agencies of Ministries of the Czech Republic

Ministry of Health, CR, - 4 grants, in 3 of these scientists of IBP participated as principal investigators

- Ministry of Agriculture, CR, - 1 grant (partial investigator from IBP)
- Ministry of Education, Youth and Sports, Program „Research Centres“ - 2 partial investigators from IBP

  - 4 grants under the Program „COST“
  - 4 grants under the Program „KONTAKT“
  - 1 project under the Program „Barrande“

From Foreign Grant Agencies

10 grants

PROGRAM I

BIOPHYSICAL CHEMISTRY OF MACROMOLECULES

LABORATORY OF BIOMACROMOLECULE PHYSICS(LBP)

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UNDERGRADUATE STUDENT:	JAN NOVÁK
BACHELORS:	DANA OHLÍDALOVÁ LUCIE VETTERLOVÁ

The study of the two-dimensional (2D) condensation of purine bases and nucleosides on the mercury and amalgam-alloy electrodes

It was found that some nucleic acid bases could form at the mercury electrode surface compact multilayers. The condensation of the second layer on the surface of the first layer can be one-dimensional with a diffusion controlled growth rate. A mathematical model of this process was made. Significant differences between adsorption behaviour of nucleotide derivatives with antiviral activity (acycloguanosine, ganciclovire) were found. It was observed that the solid amalgam electrodes (MeA) are appropriate substrates for study of the formation of the 2D condensed adlayers of purine bases and nucleosides of nucleic acids. Advantage of the MeA is that it is possible to study

the influence of the surface morphology and optical roughness of surface on the kinetics of the formation of 2D adlayer, which take place in the potential region from 0 to –2 V. In addition, the price of the amalgam electrodes is 10 time less than of the solid monocrystalline metal electrodes. The optical roughness of the amalgam – alloy electrodes is higher for each of the used metallic substrate in comparison with the unmodified metal electrodes. The overall magnitude of the optical roughness R_a of the amalgam – alloy with the thickness of about 20 nm is 0.0425 μm (AgA) to 0.0560 μm (CuA). The thick amalgam – alloy layers (order of 100 nm) have the magnitude of the optical roughness R_a from 0.0536 μm (CuA) to 0.0559 μm (PtA). These experimental results showed that the amalgam – alloy layer is smoother and more homogenously distributed on polycrystalline Cu and Ag substrates than on polycrystalline Pt substrate.
Adenosine forms in acid solution (pH 5) on the MeA, similar as at the mercury electrode, two different 2D adlayer. Both adlayers still exist on the Cu – and PtA substrates with the thickness of amalgam – alloy layer down to 20 nm. Polynucleation and growth processes taking place during of the phase transients of adenosine give rise to current maxima on the $j - t$ curves on both the Cu – and PtA substrates. During the phase transients of adenosine on the AgA only adsorption process was detected.

The rate of the phase transients of adenosine is slightly dependent on the thickness of the amalgam – alloy layer on the Cu – and PtA substrates.

The study of the adsorption of the nucleic acids at the polycrystalline metal surfaces by the optical and electrochemical methods

The change of the polarisation of the laser beam, which was reflected from the denatured (ss - DNA) and native (ds - DNA) nucleic acids treated surface of the polycrystalline metal electrode was studied by the diffractive optical element based sensor (DOE). The reference measurement was done with untreated polycrystalline metal electrodes. As working electrodes served the gold, copper and platinum polycrystalline wire. The process of the adsorption was detected by the electrochemical methods as well. The aim of the optical method using the DOE based sensor is to detect the hybridisation of the DNA on the solid metal surface from the changes of the degree of polarisation of the reflected laser beam. Detection of the hybridisation of the DNA on the metal surface by optical methods can be important for the development of the new DNA-biosensors.

Effect of low-frequency electromagnetic fields on bacteria

We have studied the effect of electromagnetic fields on bacteria. We have used a low-frequency magnetic field (f = 50Hz) with a maximum amplitude of the magnetic field induction B_m = 10mT and a microwave field of frequency f = 900 MHz (i.e. the frequency which is used in mobile phones) and output power of 0.5 W (the output power of mobile phones used to be the same or even higher). We have determined the viability of bacteria *Staphylococcus aureus* for different time of exposure (0 – 24 min) and different values of the magnetic field induction B_m (2.4 – 10 mT)**.** We have compared the growth curves of exposed and control cultures and we have followed the metabolic activity of bacteria with the tetrazolium test.

We have found, that 50 Hz magnetic field causes up to 20 % decrease of viability and metabolic activity. Microwave field causes up to 10 % decrease of the number of living bacteria. The inhibition effect was higher with longer exposure time and higher amplitude of magnetic field induction B_m. With microwave field we have observed a saturation effect.

GRANTS:

GA CR 310/01/0816
Effect of low-frequency electric and magnetic fields on biological systems
Principal investigator: V. Vetterl, 2001 – 2003

GA AS CR S5004107
Application of biophysical methods in biotechnological and clinical praxis
Principal investigator: V. Vetterl, 2001 – 2005

GA AS CR K4055109
Physics, chemistry and informatics for biological, ecological and medical applications
Principal investigator: K. Ulbrich, IMCH AS CR Prague, co-investigator: V. Vetterl, 2001 - 2004

GA AS CR KJB4004305

Chemically modified solid electrodes in electrochemical analysis of nucleic acids and their components
Principal investigator: S. Hasoň, 2003 – 2005

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In the year 2003 our work was concentrated mainly to two research fields:
Field I. Properties of nucleic acids and proteins at surfaces and their application in DNA biodetectors.
Field II. Structure and interaction of DNA and proteins in oncological research especially with respect to the protein p53.

As in the previous year, in 2003 the work in the field I was focused on electrochemistry of nucleic acids and to potentially arrayable electrochemical sensors for DNA hybridization and DNA damage which represented the main trend of work of LBCMO. In connection with newly awarded grants in 2003, the scope of the research was extended to electrochemistry of proteins and application of electrochemical methods in environmental chemistry.

Two-surface strategy in electrochemical DNA hybridization assays: Detection of osmium-labeled target DNA at carbon electrodes
Target DNAs, including a 71-mer oligonucleotide, a PCR product and a plasmid DNA, all containing oligo(A) stretches, were hybridized at magnetic Dynabeads ® oligo$(dT)_{25}$ (DBT). The hybridization events were detected using a technique based on chemical modification of the target DNA with a complex of osmium tetroxide with 2,2'-bipyridine (Os,bipy) and voltammetric detection at carbon electrodes. DNA was modified with Os,bipy prior to capture at DBT, anchored at the beads, or after release from the beads. In the latter case, DNA-Os,bipy was detected in the reaction mixture using adsorptive transfer stripping voltammetry involving extraction of unreacted Os,bipy from the electrode by organic solvents. Pre-labeling of the target plasmid DNA and the PCR product with Os,bipy significantly increased the yield of DNA captured at the beads. Tens of femtomoles of both short (the 71-mer oligonucleotide) and long (the 3-kilobase plasmid) target DNAs in a 20-microliter hybridization sample can be easily detected by means of these techniques. Various carbon electrode materials, including pyrolytic graphite (PGE), highly oriented pyrolytic graphite (HOPGE), carbon paste (CPE), glassy carbon and pencil graphite, were tested regarding their suitability for the detection of osmium-labeled DNA.

Multiple osmium-labeled reporter probes for electrochemical DNA hybridization assays. Detection of trinucleotide repeats
In electrochemical DNA hybridization assays target or probe DNAs end-labeled with electroactive compounds have been frequently used. We show that multiple osmium labels yielding faradaic (at carbon or mercury electrodes) and

catalytic signals (at mercury electrodes) can be easily covalently bound to DNA molecules. We use $(GAA)_7$ $(T)_n$ oligodeoxynucleotides (ODNs) with n ranging between 5 and 50. $(T)_n$ tails are selectively modified with osmium tetroxide,2,2'-bipyridine leaving the $(GAA)_7$ repeat intact for the DNA hybridization. These ODNs are applied as reporter probes (RP's) in DNA hybridization double-surface (DS) assay using magnetic beads for the DNA hybridization and pyrolytic graphite (PGE) or hanging mercury drop (HMDE) electrodes for the electrochemical detection. We show that in difference to the usual single-surface methods (where the RP has to be bound to target DNA near to the surface to communicate with the electrode) in the DS assay the RP can be bound to DNA regardless of its position and can used for the determination of the length of DNA repetitive sequences. Several fmols or about a hundred of amol of a RP with osmium-labeled $(T)_{50}$ tail can be detected at PGE and HMDE, respectively, at 1-2 min accumulation time.

Detecting DNA damage with a silver solid amalgam electrode

Mercury electrodes modified with supercoiled (sc) DNA have been used as highly sensitive tools for the detection of DNA strand breaks or as sensors for DNA cleaving substances. In this paper we show that silver solid amalgam electrode (AgSAE), in connection with alternating current voltammetry, provides similar information about DNA damage as the hanging mercury drop electrode. The AgSAE can be used for the detection of enzymatic or chemical DNA cleavage in solution or at the electrode surface. AgSAE modified with scDNA can be utilized as a sensor for DNA nicking substances.

Voltammetry of osmium-modified DNA at a mercury film electrode. Application in detecting DNA hybridization

Mercury film electrodes (MFE) have recently been used in nucleic acid electrochemical analysis as alternatives to the classical mercury drop ones. DNA modified with osmium tetroxide, 2,2’-bipyridine (Os,bipy) can be detected with a high sensitivity at mercury electrodes via measurements of a catalytic osmium signal. In this paper we show that mercury film on a glassy carbon electrode can be used in voltammetric analysis of Os,bipy-modified DNA. Application of the MFE as a detection electrode in double-surface electrochemical DNA hybridization assay involving osmium labeling of target DNA is demonstrated.

Voltammetric behavior of DNA modified with osmium tetroxide 2,2'-bipyridine at mercury electrodes

Osmium tetroxide complexes with nitrogen ligands (L) are probes of DNA structure and electroactive labels of DNA. Here adducts of single-stranded DNA with osmium tetroxide 2,2'-bipyridine (DNA-Os,bipy) were studied by adsorptive stripping cyclic voltammetry. It was found that at neutral pH DNA-Os,bipy produces three redox couples in the potential range between 0 and - 1 V (peaks I-III) and a cathodic peak at about –1.3 V (peak IV). This peak exhibited opposite direction in backward part of the cyclic voltammogram and peak current decreasing with increasing scan rate, suggesting its catalytic nature. We concluded that this peak corresponds to the known differential pulse voltammetric (polarograhic) peak of DNA-Os,L adducts for which catalytic hydrogen evolution is responsible. In opposite, currents of cathodic peaks II and III increased almost linearly with increasing scan rate suggesting involvement of adsorption in the electrode processes. Square-wave voltammetry was used to analyze the DNA-Os,bipy at low concentrations. It was shown that at neutral pH, peak III can offer sensitivity in the ppb range, which only little lower than that of catalytic peak IV. The latter peak is, however, superior in sensitivity at acid pH values.

Voltammetric determination of cefoperazone in a bacterial culture, pharmaceutical drug, milk and urine

Use of square-wave voltammetry (SWV) for determination of cefoperazone (CFPZ) in some buffers, bacterial culture, urine and milk is described. CFPZ provides a specific voltammetric signal, which is affected by pH and solution components. Determination of CFPZ in Britton-Robinson buffer, pH 4.4 is sensitive with low detection limit (about 0.5 nM). In a more complex medium (bacterial 2YT medium, pH 7.2) the detection limit was obtained at about 1.5 nM. We provide evidence that SWV is a suitable and quick method for CFPZ determination in a culture of living bacteria without separation of biomass. We have found big differences between methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *Staphylococcus aureus* (MSSA) in cultivation in presence of CFPZ depending on time. When CFPZ is cleaved by penicillinase, a new SWV peak b appears at more positive potentials. This peak rises both with increasing concentration of enzyme and with cleavage time while the original CFPZ peak is simultaneously decreasing. We have tried to find the concentration of CFPZ in the Pathozone drug by the standard addition method and good agreement with the declared value of CFPZ

in the drug has been found out. With a simple pre-treatment procedure it is possible to determine CFPZ in milk while in case of urine even no pre-treatment was required. Using SWV we could detect the CFPZ concentration as low as 500 nM both in bovine milk and human urine.

Application of avidin-biotin technology and adsorptive transfer stripping square-wave voltammetry for avidin in transgenic avidin maize

The proteins streptavidin and avidin were electrochemically detected in solution by adsorptive transfer stripping square wave voltammetry (AdTS SWV) at a carbon paste electrode (CPE). AdTS SWV was used to quantify biotinylated oligonucleotides, DNA hybridizations, and avidin in extracts of transgenic avidin maize. The detection limits of denatured and native streptavidin were 6 pM and 120 nM, respectively. The results demonstrated that streptavidin/avidin AdTS SWV is a sensitive and specific method for quantifying DNA, and proteins in biological samples such as foods and tissue extracts including genetically modified crops (avidin maize) and other plants in neighboring fields.

Application of elimination voltammetry to the resolution of adenine and cytosine signals in oligonucleotides. I. Homo-oligodeoxynucleotides dA_9 and dC_9

Elimination voltammetry with linear scan (EVLS) has been applied to the resolution of reduction signals of adenine and cytosine in short synthetic homo-oligodeoxynucleotides (dA_9 and dC_9). In comparison with the common electrochemical methods (linear sweep, differential pulse, and square wave voltammetry) EVLS enables to resolve the overlapped signals by using the function which eliminates the charging and kinetic currents (I_c, I_k) and conserves the diffusion current (I_d). For the adsorbed electroactive substance, this elimination function gives a well readable peak-counterpeak which has successfully been utilized to the analysis of overlapped reduction signals of adenine and cytosine on hanging mercury drop electrode (HMDE). The height and potential of signals studied were affected by the dC_9/dA_9 ratio, the time of accumulation, the stirring speed during the adsorption, and pH. Our results showed that EVLS in connection with the adsorption procedure is a useful tool for qualitative and quantitative studies of short oligonucleotides.

Electrochemical study of heavy metals and metallothionein in yeast Yarrowia lipolytica

The bioaccumulation of heavy metals (cadmium, nickel, cobalt and zinc) and the effect of these metals on the production of metallothionein and metallothionein-like proteins (MT) in Yarrowia lipolytica was studied by electrochemical methods. The concentrations of heavy metals were determined by the differential pulse voltammetry (DPV). A combination of the constant current chronopotentiometric stripping analysis (CPSA) and adsorptive transfer stripping technique (AdTS) was used to determine the content of MT in cells. Both the bioaccumulation of heavy metals and the production of MT in different cell compartments of *Yarrowia lipolytica* exposed to heavy metals were monitored. The LD50 of each metal was determined from the number of viable cells in yeast cultures: LD50Cd (37.5 μM), LD50Ni (570 μM), LD50Co (700 μM), and LD50Zn (1800 μM). The highest concentrations of heavy metals were found in the cell wall and membrane debris while the lowest concentrations were detected in cytoplasm. Cadmium and nickel showed the most significant effect on the production of MT. This study provides new insights into the ecophysiology of microorganisms and demonstrates the potential use of these electrochemical methods in the biotechnology.

In the field II our work was focused to one of the most important problems of the present molecular oncology, i.e. the structure and interactions of the tumor suppressor protein p53. Generally, this work is performed in a systematic collaboration with the Masaryk Memorial Institute of Oncology in Brno. In future years this collaboration is expected to be extended to a number of European laboratories involved in the EU project "Mutant p53" awarded to LBCMO in this year. In 2003 special attention was paid to the effect DNA supercoiling on the p53 sequence specific binding.

Enhancement of p53 sequence specific binding by DNA supercoiling

Using a new competition assay, we investigated the effect of DNA negative supercoiling on the DNA sequence specific binding (SSDB) of human wild-type (wt) p53 protein. We found that supercoiled (sc) pBluescript (pB) DNAs with different inserted p53 target sequences were stronger competitors than a mixture of scDNA pB with the given 20-mer target ODN. scDNAs were always better competitors than their linearized or relaxed forms. Two DNAs with extruded

cruciforms within the target sequence were the best competitors; removal of the cruciforms resulted in a decrease of competitor strength. In contrast to the full length wt p53, the deletion mutant p53 CΔ30 and the p53 core domain (aa 93-312) showed no enhancement of p53 SSDB to scDNA suggesting that, in addition to the p53 core domain, the C-terminal was involved in this binding. We conclude that cruciforms and DNA bends contribute to the enhancement of p53 SSDB to scDNA and that the DNA supercoiling is an important determinant in the p53 sequence specific binding. Supercoiling may thus play a significant role in the complex p53 regulatory network.

Recognition of DNA modified by antitumor cisplatin by "latent" and "active" protein p53

Tumor suppressor protein p53 possesses two DNA-binding sites. One that is located within its core domain is responsible for sequence-specific DNA binding of the protein, non-specific binding to internal segments of single- or double-stranded DNA, and to certain kinds of non-B DNA structures. The other that is contained in the C-terminus of the protein binds to damaged DNA. Binding of active, latent, and *in vitro*-activated p53 protein to DNA fragments modified by antitumor cisplatin was studied using electrophoretic mobility shift assay in agarose gels and immunoblotting analysis. We found that both latent and active p53 forms bound to random sequences of DNA globally modified by cisplatin with a higher affinity than to unmodified DNA. Interestingly, the latent form exhibited a more pronounced selectivity for platinated DNA than the active p53. Consistently with this observation, the preference of the latent form for platinated DNA decreased as a consequence of the activation of latent p53 by phosphorylation at the protein kinase C site within its C-terminus or by binding of the monoclonal antibody Bp53-10.1. Competition experiments involving a 20-bp consensus sequence of p53 suggested that the p53 core domain was a primary binding site of the active p53 when it bound to DNA fragments lacking consensus sequence, but modified by cisplatin. In addition, the latent protein was found to selectively interact with DNA modified by cisplatin probably *via* its C-terminus.

GRANTS:

GA AS CR A4004110
Binding of tumor suppressor protein p53 to DNA. The influence of DNA superhelicity and posttranslational modifications of the protein
Principal investigator: E. Paleček, 2001 - 2004

GA AS CR A4004108
Development of electrochemical biosensors for DNA damage
Principal investigator: M. Fojta, 2001 - 2003

GA AS CR A1163201
Application of adsorptive transfer and elimination techniques in oligonucleotides and nucleic acids research
Principal investigator: F. Jelen, 2002 - 2004

GA AS B5004203
Regulation of transcription factors binding to consensus sequences in superhelical DNA. Influence of phosphorylation of tumor supressor proteins p53, p73 and SMAD4 to their binding activity
Principal investigator: V. Brázda, 2002 - 2004

GA AS CR KJB4004302

Application of chemical structural probes and electroanalytical methods in DNA damage detection. Development of DNA sensors

Principal investigator: L. Havran, 2003 - 2005

GA AS CR IBS5004355
Possibilities of electrochemical methods in genomics.
Basis for development of DNA sensors.
Principal investigator: E. Paleček, 2003 - 2005

GA AS CR S5004009
Untraditional therapeutic approaches in oncology
Principal investigator: A. Kozubík, principal co-investigator: E. Paleček, 2000 - 2004

GA AS CR K4055109
Physics, chemistry and informatics for biology, ecology and health application
Principal investigator: K. Ulbrich, IMC AS CR Prague, principal co-investigator: E. Paleček, IBP AS CR, Brno, 2001 – 2004

GA AS CR S5004107
Applications of biophysical methods in biotechnological and clinical praxis
Principal investigator: V. Vetterl, co-investigator: E. Paleček, 2001 - 2005

GA CR 301/00/D001
Binding of human and mouse tumor suppressor protein p53 to linear and supercoáiled DNAs
Principal investigator: V. Brázda, 2000 - 2003

GA CR 204/00/D49
Influence of chemical modification of DNA and synthetic oligonucleotides on their electrochemical behavior.
Principal investigator: L. Havran, 2000 - 2003

GA CR 301/02/0831
Interaction of protein p53 and its homologues with DNA and their role in malignant tranformation
Principal investigator: B. Vojtěšek, MIO Brno, principal co-investigator: E. Paleček, 2002 - 2004

GA CR 204/02/0734
Interactions of tumor suppressor proteins with DNA. Roles of DNA structure and protein modifications
Principal investigator: M. Fojta, 2002 - 2004

GA CR 203/02/0422
New trends in electrochemistry of nucleic acids and their applications in environmental chemistry
Principal investigator: F. Jelen, 2002 - 2004
GA CR 204/03/0566
Electrochemistry in protein analysis and in detection of DNA hybridization
Principal investigator: E. Paleček, 2003 - 2005

IGA MH CR NC/7574 - 3
Recognition of DNA damage by tumor suppressor proteins. Effects of anti-cancer drugs
Principal investigator: M. Fojta, 2003 - 2005

LABORATORY OF STRUCTURE AND DYNAMICS OF NUCLEIC ACIDS (LSDNA)

HEAD: doc. RNDr. Jiří Šponer, DrSc.

SCIENTISTS: Mgr. Naďa Špačková
Judit E. Šponer, Ph.D.

The main focus of research are large-scale investigations of structure and dynamics of DNA and RNA molecules with the aid of state-of-the-art computer simulations (molecular dynamics, MD) combined with other advanced methods such as non-empirical molecular orbital calculations, crystal database studies, and others.

Extended MD analysis aimed to describe the kinetic intermediates participating in formation of guanine quadruplex (G-DNA) molecules was carried out. The simulations were supplemented by thermodynamics free energy calculations and provided unique insights into the folding path of G-DNA.

Intense ab initio quantum chemical investigations were carried out on metal cation binding to nucleic acids. The studies revealed, among other things, major polarization effects contributing to a binding of hydrated divalent metal cations to nucleotides. Systematic analysis was performed to relate gas phase properties of metal-nucleobase complexes with important condensed phase properties such as the acid/base equilibria of metalated nucleobases and their base pairing association constants.

Broad studies of non-Watson-Crick RNA motifs observed in ribosome crystals continued and included motifs such as the 23S rRNA K-turns, 5S rRNA Loop E and others. Three dimensional structure of Loop E of chloroplast has been predicted in absence of atomic resolution experiments based on a homology modeling and MD simulations. Combined quantum chemical, crystal database and phylogenetic analysis of cis-Watson Crick A/G base pairs revealed that their conservation patterns are determined primarily by out-of-plane and tertiary interactions involving the guanine amino group. This is for the first time that a clear direct link was demonstrated between the details of electronic structure of nucleobases (amino group pyramidalization in this case) and the RNA conservation patterns.

GRANTS:

MEdYS CR LN00A016
Program „Research Centres“, Biomoolecular Centre
Head: J. Šponer
Principal investigator, J. Koča, Fac. Sci. MU Brno, co-investigator: J. Šponer, 2000 - 2004

PROGRAM II

BIOPHYSICS OF NUCLEIC ACIDS COMPLEXES

LABORATORY OF MOLECULAR BIOPHYSICS AND PHARMACOLOGY (LMBP)

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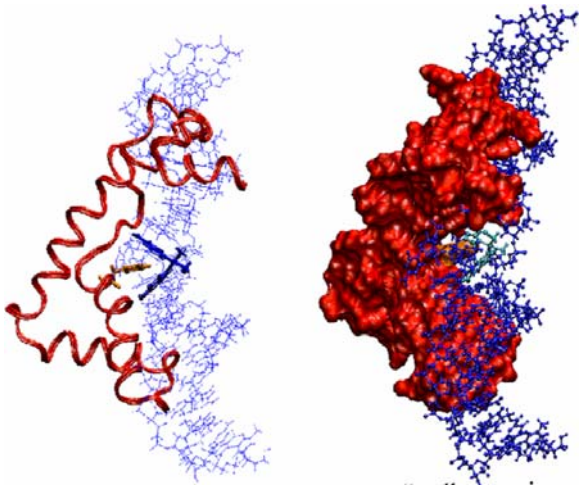
Recognition of DNA interstrand cross-link of antitumor cisplatin by HMGB1 protein

Several proteins that specifically bind to DNA modified by cisplatin [*cis*-diamminedichloroplatinum(II)], including those containing high-mobility-group (HMG)-domains, mediate antitumor activity of this drug. Oligodeoxyribonucleotide duplexes containing a single, site-specific interstrand cross-link of cisplatin were probed for recognition by the rat chromosomal protein HMGB1 and its domains A and B using the electrophoretic mobility-shift assay. It has been found that the full-length HMGB1 protein and its domain B to which the lysine-rich region (seven amino acid residues) of the A/B linker is attached at the N-terminus (the domain HMGB1b7) specifically recognize DNA interstrand cross-linked by cisplatin. The affinity of these proteins to the interstrand cross-link of cisplatin is not very different from that to the major 1,2-GG intrastrand cross-link of this drug. In contrast, no recognition of the interstrand cross-link by the domain B lacking this region or by the domain A with or without this lysine-rich region attached to its C-terminus is noticed under conditions when these proteins readily bind to 1,2-GG intrastrand adduct. A structural model for the complex formed between the interstrand cross-linked DNA and the domain HMGB1b7 was constructed and refined using molecular mechanics and molecular dynamics techniques. The calculated accessible areas around the deoxyribose protons correlate well with the experimental hydroxyl radical footprint. The model suggests that the only major adaptation necessary for obtaining excellent surface complementarity is extra DNA unwinding (~40°) at the site of the cross-link. The model structure is consistent with the hypothesis that the enhancement of binding affinity afforded by the basic lysine rich A/B linker is a consequence of its tight binding to the sugar-phosphate backbone of both DNA strands.



Complex formed between HMGB1b7 domain and DNA, with the cis-platin interstrand bridge

Formation of platinated GG cross-links on DNA by photoactivation of a Pt(IV) azide complex

Platinum(II) diam(m)ine complexes such as cisplatin are effective anticancer drugs but have accompanying side-effects. We are exploring the design of platinum complexes with low toxicity that could be photoactivated selectively at the target site. We show here that the Pt(IV) azide complex *cis,trans*-$[Pt(en)(N_3)_2(OH)_2]$ is unreactive towards DNA until irradiated with visible light. Transcription mapping studies of a 212-bp fragment of pSP73KB plasmid DNA treated with *cis,trans*-$[Pt(en)(N_3)_2(OH)_2]$ and irradiated with visible light showed that the platination sites were similar to those observed for cisplatin, and were mainly in GG sequences. HPLC analysis of enzymatic digests of an irradiated sample of a 40-bp DNA duplex treated with the same complex also revealed preferential formation of GG cross-links. Since such DNA lesions are thought to be responsible for the induction of apoptosis in cancer cells by platinum drugs, the use of unreactive photoactivatable platinum pro-drugs may become an effective strategy for the design of a new generation of platinum anticancer complexes.

DNA binding mode of the cis and trans geometries of new antitumor nonclassical platinum complexes containing piperidine, piperazine or 4-picoline ligand in cell-free media. Relations to their activity in cancer cell lines

The global modification of mammalian and plasmid DNAs by novel platinum compounds, *cis*- or *trans*-$[PtCl_2(NH_3)(Am)]$, where Am = NH_3, nonplanar heterocycle piperidine or piperazine and aromatic planar heterocycle 4-picoline was investigated in cell-free media using various biochemical and biophysical methods. These modifications have been compared with activity of these new compounds in several tumor cell lines including those resistant to cisplatin. The results show that the replacement of the NH_3 group in cisplatin by the heterocyclic ligands does not considerably affect DNA binding mode of this drug. Cytotoxicity studies have revealed that the replacement lowers activity of the platinum compound in both sensitive and resistant cell lines. It has been suggested that the reduced activity of these analogues of cisplatin is associated with some features of the damaged DNA and/or its cellular processing. Alternatively, the reduced activity of the analogues of cisplatin might be also due to the factors that do not operate directly at the level of the target DNA, such as intracellular platinum uptake. In contrast to the analogues of cisplatin, the replacement of one ammine group by the heterocyclic ligand in its clinically

ineffective trans isomer (transplatin) results in a radical enhancement of its activity in tumor cell lines. Importantly, this replacement also markedly alters DNA binding mode of transplatin. The results support the view that one strategy how to activate trans geometry in bifunctional platinum(II) compounds including circumvention of resistance to cisplatin may consist in a chemical modification of the ineffective transplatin which results in an increased stability of its intrastrand cross-links in double-helical DNA and/or in an increased efficiency to form interstrand cross-links.

Effects of a piperidine ligand on DNA modification by antitumor cisplatin analogues

Replacement of the ammine group in antitumor cisplatin by a heterocyclic ligand (piperidine, piperazine, 4-picoline) results in reduction of cytotoxicity in human ovarian cancer cells. In order to shed light on the reduced potency of these analogues we examined conformation of oligodeoxyribonucleotide duplexes containing a cross-link of *cis*-[$PtCl_2(NH_3)$(piperidine)], their recognition by HMG proteins and nucleotide excision repair. The replacement does not affect DNA binding mode including conformational alterations and excission of the cross-links. The results suggest that in certain cancer cells the lower cytotoxicity of *cis*-[$PtCl_2(NH_3)$(piperidine)] is partially associated with the reduced affinity of the HMG proteins to the major intrastrand cross-links of this analogue relative to the same adducts of cisplatin. The reduced intracellular accumulation with subsequent effects on the level of DNA platination in the cells also contributes to the reduced cytotoxicity of *cis*-[$PtCl_2(NH_3)$(piperidine)].

Activation of trans geometry in bifunctional mononuclear platinum complexes by a piperidine ligand. Mechanistic studies on antitumor action

Paradigm for the structure-pharmacological activity relationship of bifunctional platinum antitumor drugs is that transplatin is clinically ineffective. To this end, however, several new complexes of the trans structure have been identified which exhibit cytotoxicity in tumor cells that is even better than that of the analogous cis isomers. As mentioned above the replacement of one ammine ligand by the heterocyclic ligand, such as piperidine, piperazine or 4-picoline in the molecule of transplatin resulted in a radical enhancement of its cytotoxicity. We examined oligodeoxyribonucleotide duplexes bearing a site-specific cross-link of the transplatin analogue containing the piperidine ligand by biochemical methods. The results indicate that in contrast to transplatin *trans*-[$PtCl_2(NH_3)$(piperidine)] forms stable 1,3-intrastrand cross-links in double-

helical DNA which distort DNA and are not readily removed from DNA by nucleotide excision repair system. Hence, the intrastrand cross-links of *trans*-[$PtCl_2(NH_3)$(piperidine)] could persist for a sufficiently long time potentiating its toxicity toward tumor cells. *trans*-[$PtCl_2(NH_3)$(piperidine)] also forms in DNA minor interstrand cross-links which are similar to those of transplatin so that these adducts appear less likely candidates for genotoxic lesion responsible for antitumor effects of *trans*-[$PtCl_2(NH_3)$(piperidine)]. Hence, the role of structurally unique intrastrand cross-links in the antitumor effects of transplatin analogues in which one ammine group is replaced by a heterocyclic ligand may predominate.

DNA-protein cross-linking by trans-[$PtCl_2$(E-iminoether)$_2$]. A concept for activation of the trans geometry in platinum antitumor complexes

We have shown recently that the replacement of ammine ligands by iminoether in transplatin (*trans*-[$PtCl_2(NH_3)_2$]) results in a marked enhancement of its cytotoxicity so that it is more cytotoxic than its *cis* congener and exhibits significant antitumor activity including activity in cisplatin-resistant tumor cells. In addition, we have also shown previously that this new trans compound (*trans*-[$PtCl_2$(*E*-iminoether)$_2$]) forms mainly monofunctional adducts at guanine residues on DNA, which is generally accepted to be the cellular target of platinum drugs. In order to shed light on the mechanism underlying the antitumor activity of *trans*-[$PtCl_2$(*E*-iminoether)$_2$] we examined oligodeoxy-ribonucleotide duplexes containing a single, site-specific, monofunctional adduct of this transplatin analogue by the methods of molecular biophysics. The results indicate that major monofunctional adducts of *trans*-[$PtCl_2$(*E*-iminoether)$_2$] locally distort DNA, bend DNA axis by 21° toward the minor groove, are not recognized by HMGB1 proteins, and are readily removed from DNA by nucleotide excision repair system. In addition, the monofunctional adducts of *trans*-[$PtCl_2$(*E*-iminoether)$_2$] readily cross-link proteins, which markedly enhances the efficiency of this adduct to terminate DNA polymerization by DNA polymerases *in vitro* and to inhibit removal of this adduct from DNA by nucleotide excision repair system. It is suggested that DNA-protein ternary cross-links produced by *trans*-[$PtCl_2$(*E*-iminoether)$_2$] could persist considerably longer than the non-cross-linked monofunctional adducts, which would potentiate toxicity of this antitumor platinum compound toward tumor cells sensitive to this drug. Thus, *trans*-[$PtCl_2$(*E*-iminoether)$_2$] represents a quite new class of platinum antitumor drugs in which activation of trans geometry is associated with an increased efficiency to form DNA-protein

ternary cross-links thereby acting by a different mechanism than "classical" cisplatin and its analogues.

DNA binding by antitumor trans-[$PtCl_2(NH_3)$(thiazole)]. Protein recognition and nucleotide excision repair of monofunctional adducts

The monofunctional lesions represent a significant fraction of stable adducts formed in DNA by bifunctional antitumor trans-platinum compounds with planar ligands. Therefore, we also analyzed short DNA duplexes containing the single, site-specific monofunctional adduct of a representative of this class of platinum drugs, antitumor trans-[$PtCl_2(NH_3)$(thiazole)]. It has been shown that in contrast to the adducts of monodentate chlorodiethylenetriamineplatinum(II) chloride or [$PtCl(NH_3)_3$]Cl, the monofunctional adduct of trans-[$PtCl_2(NH_3)$(thiazole)] inhibits DNA synthesis and creates a local conformational distortion similar to that produced in DNA by the major 1,2-GG intrastrand cross-link of cisplatin which is considered the lesion most responsible for its anticancer activity. In addition, the monofunctional adducts of trans-[$PtCl_2(NH_3)$(thiazole)] are recognized by HMGB1 domain proteins and removed by the nucleotide excision repair system similarly as the 1,2-GG intrastrand cross-link of cisplatin. The results of the present work further support the view that the simple chemical modification of structure of an inactive platinum compound alters its DNA binding mode into that of an active drug and that processing of the monofunctional DNA adducts of the trans-platinum analogues in tumor cells may be similar to that of the major bifunctional adducts of “classical” cisplatin.

Melting of cross-linked DNA. Cross-linking effect caused by local stabilization of the double helix

DNA interstrand cross-links are usually formed due to bidentate covalent or coordination binding of a cross-linking agent to nucleotides of different strands. However, interstrand linkages can be also caused by any type of chemical modification that gives rise to a strong local stabilization of the double helix. These stabilized sites conserve their helical structure and prevent local and total strand separation at temperatures above the melting of ordinary AT and GC base pairs. This local stabilization makes DNA melting fully reversible and independent of strand concentration like ordinary covalent interstrand cross-links. The stabilization can be caused by all the types of chemical modifications (interstrand cross-links, intrastrand cross-links or monofunctional adducts) if they give rise to a strong enough local stabilization of the double helix. Our

calculation demonstrates that an increase in stability by 25 to 30 kcal in the free energy of a single base pair of the double helix is sufficient for this "cross-linking effect"(i.e.conserving the helicity of this base pair and preventing strand separation after melting of ordinary base pairs). For the situation where there is more then one stabilized site in a DNA duplex (e.g., 1 stabilized site per 1000 base pairs), a lower stabilization per site is sufficient for the "cross-linking effect " (18 -20 kcal). A substantial increase in DNA stability was found in various experimental studies for some metal-based antitumor compounds. These compounds may give rise to the effect described above. If ligand induced stabilization is distributed among several neighboring base pairs, a much lower minimum increase per stabilized base pair is sufficient to produce the cross-linking effect (1 bp-24.4 kcal; 5 bp-5.3 kcal; 10 bp-2.9 kcal, 25 bp-1.4 kcal; 50 bp-1.0 kcal). The relatively weak non-covalent binding of histones or protamines that cover long regions of DNA (20-40 bp) can also cause this effect if the salt concentration of the solution is sufficiently low to cause strong local stabilization of the double helix. Stretches of GC pairs more than 25 bp in length inserted into poly(AT) DNA also exhibit properties of stabilizing interstrand cross-links.

DNA interactions of monofunctional organometallic ruthenium(II) antitumor complexes in cell-free media

Modifications of natural DNA in a cell-free medium by antitumor monodentate Ru(II) arene compounds of the general formula $[(\eta^6\text{-arene})Ru(en)Cl]^+$ (arene = biphenyl, dihydroanthracene, tetrahydroanthracene, *p*-cymene or benzene; en = ethylenediamine) were studied by atomic absorption, melting behavior, transcription mapping, circular and linear dichroism, plasmid unwinding, competitive ethidium displacement and differential pulse polarography. The results indicate that these complexes bind preferentially to guanine residues in double-helical DNA. The data are consistent with DNA binding of the complexes containing biphenyl, dihydroanthracene or tetrahydroanthracene ligands that involves combined coordination to G N7 and non-covalent, hydrophobic interactions between the arene ligand and DNA, which may include arene intercalation and minor groove binding. In contrast, the single hydrocarbon rings in the *p*-cymene and benzene ruthenium complexes cannot interact with double-helical DNA by intercalation. Interestingly, the adducts of the complex containing *p*-cymene ligand, which has methyl and isopropyl substituents, distort the conformation and thermally destabilize double-helical

DNA distinctly more than the adducts of the three multi-ring ruthenium arene compounds. It has been suggested that the different character of conformational alterations induced in DNA, and resulting thermal destabilization, may affect differently further "downstream" effects of damaged DNA, and consequently may result in different biological effects of this new class of metal-based antitumor compounds. The results point to a unique profile of DNA binding for Ru(II) arene compounds, suggesting that a search for new anticancer compounds based on this class of complexes may also lead to an altered profile of biological activity in comparison with metal-based antitumor drugs already used in the clinic or currently on clinical trials.

GRANTS:

GA CR 305/02/1552A
Platinated oligonucleotides for selective modulation of gene expression, relations to antisense strategy and development of new drugs
Principal investigator: V. Brabec, 2002 - 2004

GA CR 202/01/D110
Microcalorimetric analysis of thermodynamic stability of DNA affected by anticancer platinum complexes
Principal investigator: C. Hofr, 2001 - 2004

GA CR 204/03/H016
Structural biophysics of macromolecules
Principal investigator: V. Brabec, 2003 - 2007

GA AS CR A5004101
Structure, recognition and biochemistry of DNA modified by antitumor platinum drugs
Principal investigator: V. Brabec, 2001 - 2005

GA AS CR KJB5004301
Molecular mechanisms underlying anticancer effects of a new drug BBR3464
Principal investigator: J. Kašpárková, 2003 - 2005

IGA MEdYS CR 1K03010
A study of thermodynamic stability of DNA modified by new antitumor platinum complexes
Principal investigator: V. Brabec, 2003 - 2005

LABORATORY OF DNA MOLECULAR COMPLEXES (LADMC)

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Laboratory is focused on structure-function relationships in complexes of proteins and nucleic acids which participate in metabolism of genetic material. Within this focus, a specific attention is paid to analysis of eukaryotic chromosome ends (telomeres), to the study of their synthesis by means of telomerase or so called alternative mechanisms, and to the isolation and characterisation of telomere-binding proteins. While this research in plants is of basic science nature, in human cells and clinical samples the research is targeted to the field of molecular diagnostics.

Analysis of the structure of typical and alternative telomeres has shown that in a phylogenetically distinct clade of monocotyledonous plants within the order Asparagales, "typical" Arabidopsis-type telomeres (TTTAGGG)n have been replaced by variant telomeric sequences, the vertebrate (TTAGGG)n sequence

being the most abundant. Accordingly, telomerases of those plant species show a high error rate (25%) during in vitro telomere synthesis in contrast to telomerases synthesizing the "typical" plant telomeres. The only exception makes the family *Alliaceae*, in which both types of telomeres, as well as any of the other known variants of telomeric repeats are absent. The telomerase activity has not been found in this family too. The absence of activity is not due to a presence of telomerase inhibitors, as shown by admixture experiments with telomerase extracts of other plants.

Similar studies in the dicotyledonous plant family of Solanaceae have shown that members of the genus *Cestrum* and of closely related genera *Vestia* and *Sessea* lack telomeres of both *Arabidopsis* and vertebrate type, although short interstitial telomeric sequences (ITSs) occur scattered throughout the genome in both orientations. To isolate candidate telomeric sequences in *Cestrum* we assumed that some of the ITSs were residues of the original telomeres and that they may still be located in the vicinity of present-day telomeres. Three sequence types associated with ITSs were cloned and characterized; these were termed NA3G, BR23 and A/T-rich minisatellite. These high copy number sequences are dispersed across the genome and clustered at a number of chromosomal loci. Their association with ITSs, which can act as recombination hotspots, might indicate past recombination and chromosomal fusion events, processes that may have contributed to the large size of *Cestrum* chromosomes. The sequences are frequently arranged as NA3G-ITS-BR23 blocks embedded in an A/T-rich minisatellite array. The A/T-rich minisatellite is of particular interest because the consensus 5′-$T_{4–5}$AGCAG-3′ might be a derivative of "typical" eukaryotic telomeric sequence motifs. The sequence is abundant at the end of some chromosomes in *C. parqui* and is found not only in *Cestrum* but also in the closely related genera *Sessea* and *Vestia*, which also lack *Arabidopsis*-type telomeric sequences. However, the sequence is absent from the Solanaceae genera investigated that are outside the group, including the closely related genus *Streptosolen*, which all have the *Arabidopsis*-type telomere. The data indicate that the A/T rich minisatellite might have evolved in response to the loss of *Arabidopsis*-type telomeres.

The study of protein components of plant telomeres resulted in characterisation of two candidate telomere-binding proteins from *A. thaliana*. Both proteins termed AtTBP2 and AtTBP3 contain a single Myb-like DNA-binding domain at the N-terminus, and a histoneH1/H5-like DNA-binding domain in the middle of the protein sequence. Both proteins are expressed in various A. thaliana tissues. Using the two-hybrid system interaction between the proteins AtTBP2 and

AtTBP3 and self-interactions of each of the proteins were detected. Each of the two proteins is able to bind specifically the G-rich strand and double-stranded DNA of plant telomeric sequence. None of the proteins alone or their mixture affects telomerase activity in vitro. Correspondingly, no interaction was observed between any of two proteins and the *Arabidopsis* telomerase reverse transcriptase catalytic subunit.

Within a research of diagnostic use of telomere and telomerase analysis, development and optimization of specific *in situ* techniques (EDF-FISH, dideoxy-PRINS) has been performed to discriminate tumour cells which use telomerase for telomere maintenance, from those using alternative recombination mechanism.

Besides, a technique has been established for determination of telomerase activity – a dual-colour real-time telomeric repeat amplification protocol (DC-RQ-TRAP). The use of this technique is faster and cheaper than classical TRAP, as it avoids time-consuming post-amplification procedures (polyacrylamide gel electrophoresis, staining, imaging and image analysis). All the data for quantification are provided directly by real-time PCR software. Both false-positive and false-negative can be suppressed directly based on amplification curves of the sample and internal control, which is amplified in the same test-tube. Moreover the technique provides more reliable results, as the source data for quantification – the critical or threshold cycles - are collected during exponential phase of the reaction, while in the classical evaluation based on the total product generated the data come from the platteau phase, which may be limited by any reaction component which becomes depleted.

GRANTS:

GA CR 204/02/0027
Molecular analysis of the structure and function of typical and alternative telomeres in plants
Principal investigator: J. Fajkus, 2002 - 2004

IGA MH CR NC7043-3
Telomerase activity as a new prognostic factor in multiple myeloma
Principal investigator. R. Hájek, co-investigator: J. Fajkus, 2002 - 2004

GA AV CR S5004010
Development of novel diagnostic techniques for oncology
Principal investigator: S. Kozubek, co-investigator: J. Fajkus, 2000 - 2004

NAZV1164 Characterization of potato genotypes by DNA fingerprinting method
Principal investigator: H. Polzerová, co-investigator: J. Fajkus, 2001 - 2004

IGF16/01 (University hospital Brno)
Research of prognostic factors in multiple myeloma,
Principal investigator: R. Hájek, co-investigator: J. Fajkus, 2001 - 2003

143100008 IGA MEdYS CR (Research project of MU)
Genomes and their function
Principal investigator: J. Relichová, co-investigator: J. Fajkus, 1999-2004

AV0Z5004920
Biophysical properties of living systems
Principal investigator: J. Šlotová, co-investigator: J. Fajkus, 1999 - 2004

GA AS CR K5011112
Molecular and cellular basis of severe disorders
Principal investigator: P. Mareš, IPH AS CR Prague, co-investigator: J. Fajkus, 2001 - 2004

LABORATORY OF ANALYSIS OF CHROMOSOMAL PROTEINS (LACP)

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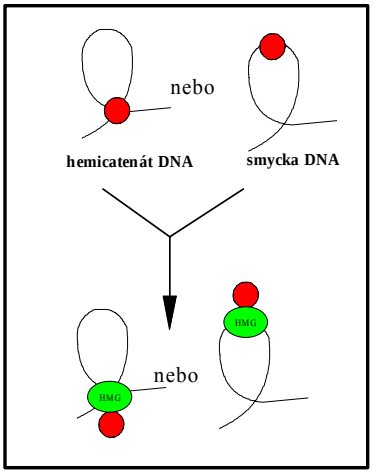
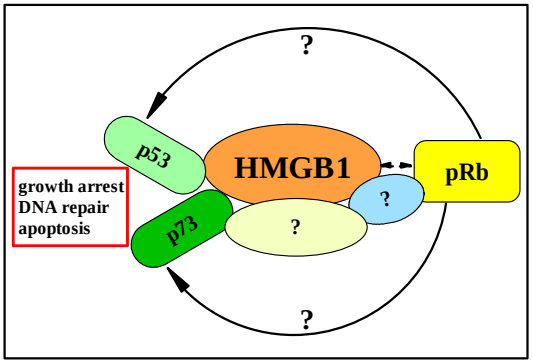
We studied the mechanism of specific recognition of hemicatenate DNA loops (hcDNA) due to the effect of the tumor suppressor protein p53. High affinity of p53 to hcDNA resulted from the preferential binding of p53 to the region of crossing of DNA strands.
Chromosomal protein HMGB1 had the capacity to displace the DNA-bound p53 by forming ternary complexes hcDNA-p53-HMGB1, probably due to direct interactions protein-protein (Fig.1).



Mechanism of binding of p53 to hemicate DNA (hcDNA) and displacement of p53 from the DNA due to the chromosomal protein HMGB1. Red circles, p53. green ellipse, HMGB1

Binding of p53 to hcDNA did not cause any significant auto-degradation of p53. This finding may reveal that p53 did not recognize hcDNA as a damaged region, but as a natural binding region (hypothesis).
Using the method of transient transfection of tumor cell lines ($p53^{-/-}$, $Rb^{-/-}$) we could demonstrate significant stimulation of transactivating capacity of proteins of the family p53 by the retinoblastoma protein (pRb). The expression of HMGB1 in these cells blocked the effect of pRb on the function of p53 as transcription activators. This is a basis for the hypothesis that will determine further experiments in the Laboratory and experiments in collaborating laboratory in Japan. (Fig.2).



Hypothetical function of HMGB as a link between the tumor suppressor protein p53 and the retinoblastoma protein

GRANTS:

GA CR 301/02/0952
Tumor supressor proteins of p53 family and chromosomal protein HMGB1. A study of a functional consequence
Principal investigator: M. Štros, 2002 - 2004

GA AS CR A5004105
Understanding of DNA binding by RNA polymerase I transcription factor xUBF to DNA
Principal investigator: M. Štros, 2001 - 2003

GA AS CR K4055109
Physics, chemistry and informatics for biological, ecological and medical applications
Principal investigator: K. Ulbrich, IMCH AS CR Prague, co-investigator:
M. Štros, 2001 - 2004

PROGRAM III

BIOPHYSICS AND BIOINFORMATICS OF GENOMES

LABORATORY OF CD SPECTROSCOPY OF NUCLEIC ACIDS (LSNA)

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	MGR. KLÁRA BEDNÁŘOVÁ
	ING. OLGA BOBROVÁ
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TECHNICAL ASSISTANT:	JITKA HEGROVÁ
GRADUATE STUDENTS:	MGR. MICHAL ZEMÁNEK
	MARKÉTA FIALOVÁ
UNDERGRADUATE STRUDENT:	MARTIN SCHWARZER

A dominant part of the human genome is composed of long DNA stretches containing repeated simple sequential motifs of bases. These motifs frequently expand in genomes, while these expansions correlate in some cases with the incidence of serious, namely neurodegenerative, diseases. The source of the expansions is probably associated with anomalous conformational properties of these DNA regions.

By means of CD and absorption spectroscopies and polyacrylamide gel electrophoresis we have studied conformational properties of $(CCA)_n$ a $(TGG)_n$ oligonucleotides with n=4, 7, and 8. We found that, depending on ionic strength, type of cations and pH, the individual oligonucleotide chains were able to form ordered homostructures. The $(TGG)_n$ strands formed hairpins [$(TGG)_7$ a $(TGG)_8$] and homoduplexes [$(TGG)_4$] at low ionic strength. In the presence of potassium cations, all the $(TGG)_n$ were transformed into tetraplex arrangements. The complementary $(CCA)_n$ strands were random coils at slightly alkaline pH values while acidification transformed them into bimolecular intercalated tetraplexes even in the vicinity of neutral pH. In addition, $(CCA)_7$ and $(CCA)_8$ formed these tetraplexes intramolecularly. The complementary $(TGG)_n$ and $(CCA)_n$ strands willingly provided classical duplexes even under conditions when the single strands adopted ordered homostructures. Thus, the particular $(TGG)_n$ and $(CCA)_n$ strands can form the homostructures only in the absence of their complement. The appearance of the homostructures, e.g. during DNA replication, may be responsible for the fact that the $(TGG)_n/(CCA)_n$ motif is the most polymorphic microsatellite of the human genome.

Alternating $(GA)_n$ sequences are frequently found in promoter regions of higher eukaryote genes. They are characterized by an extreme conformational polymorphism. Apart from a regular duplex with the complementary strand $(TC)_n$, and the $(TC)_n.(GA)_n.(TC)_n$ and $(GA)_n.(TC)_n$ $.(GA)_n$ triplexes, they also form

homostructures. With the aid of the above-mentioned techniques, we studied the influence of a three-cytosine block connected to the 5′- or 3′- end to the $(GA)_5$ fragment on its conformational behaviour. In low ionic strength solutions of neutral pH, all the three fragments were random single strands. In the vicinity of pH 5, acidification brought about a cooperative transition of $(GA)_5$ into an ordered single strand. In the same pH region $(GA)_5C_3$ underwent a conformational transition, while, however, the resulting structure was a tetraplex. $C_3(GA)_5$ also formed a tetraplex, but the four-stranded structure already appeared around pH 7. Our results further indicate that, in the case of $(GA)_5C_3$, the strand association concerned only cytosines, forming an intercalated tetraplex, whereas the $(GA)_5$ blocks remained ordered single strands. In the case of $C_3(GA)_5$, the $(GA)_5$ block adopted a guanine tetraplex. Its formation was enabled by hemiprotonated cytosine pairs as $(GA)_5$ did not form tetraplex under any conditions. The ordered $(GA)_n$ single strand was also formed at neutral pH in the presence of ethanol. The ethanol-stabilized conformer was destabilized by the block of cytosines connected at any side of the molecule. Increasing ionic strength transformed all the three oligonucleotides into a homoduplex with parallel orientation of strands.

We further studied a set of DNA fragments, differing in length and containing the human telomere sequence, namely G_3, $TTAG_3$, G_3TTA, G_3TTAG_3, $(G_3TTA)_3G_3$, and $(G_3TTA)_7G_3$, to find out the stability of their tetraplex arrangements. We found that $TTAG_3$, similar to G_3, formed a four-molecular tetraplex whose arrangement and stability were not influenced by the TTA triplet. The insertion of TTA triplet on the 3′- end of the G_3 block markedly affected its conformational properties. The CD spectra of G_3TTA surprisingly indicated that the four-stranded tetraplexes may adopt not only parallel but also antiparallel orientation of the strands. Electrophoresis also provided two bands corresponding to four-molecular associations. The G_3TTA tetraplex was markedly more thermostable than that of the G_3 block. The G_3TTAG_3 fragment formed a bimolecular tetraplex while, again, its CD spectra and two electrophoretic bands suggested its two distinct arrangements. The population of the two tetraplex conformers changed depending on solvent conditions and the sample history. $(G_3TTA)_3G_3$ and $(G_3TTA)_7G_3$ permanently adopted an intramolecular tetraplex, even in the absence of K^+ ions or at low salt. Both the oligonucleotides have similar stability, yet it seems that the TTA triplets present between two tetraplex blocks rather destabilized the structure. The sequence $(G_3TTA)_3G_3$ represents the optimal length for tetraplex formation: the tetraplex folds intramolecularly, it is markedly more stable than tetraplexes of shorter sequences and at least as stable as those of longer sequences. The stability of duplexes, on the contrary, distinctly increases with the length of the molecule. Moreover, contrary to intermolecular tetraplexes, the kinetics of melting and also formation of the intramolecular $(G_3TTA)_3G_3$ tetraplex is fast, which again is an important property for the possibility of its formation *in vivo*.

GRANTS:

GA CR 204/01/0561

Conformational polymorphy of DNA molecules containing trinucleotide repeats in connection with genetic diseases
Principal investigator: M. Vorlíčková, 2001 - 2003

GA AS CR A4004201
DNA tetraplees and their occurrence in the human genome
Principal investigator: M. Vorlíčková, 2002 - 2006

GA AS CR K5052113

Structure, expression and interaction of genomes
Principal investigator: V. Pačes, IMG AS CR Prague, co-investigator:
M. Vorlíčková, 2001 - 2004

LABORATORY OF DNA BIOPHYSICS AND GENOME BIOINFORMATICS (LDBGB)

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	MGR. PETR HANZÁLEK, PH.D.
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	MGR. NAĎA PAŘÍZKOVÁ
	ING. JITKA VONDRUŠKOVÁ
	MGR. MARTIN VÝKRUTA
TECHNICAL ASSISTANT:	SOŇA KAŠKOVÁ
GRADUATE STUDENT:	MGR. IVANA VASILENKOVÁ

The Laboratory explores principles of primary, secondary and tertiary structures of genomic molecules of DNA, restriction and PCR fragments and synthetic oligonucleotides using spectroscopic, electrophoretic, photochemical, PCR and computer methods. The aim is to find out how the genomic molecules of DNA arose, how they function and how they undergo changes.

We performed a bioinformatic analysis of the human and mouse genomes. We found a stretch of 1040 consecutive AT pairs in the human genome. The human genome furthermore contains more than 120 AT stretches longer than 300 bp. Such long stretches should have biophysical properties (thermostability, bends, grooves width of the double helix) qualitatively different from the surrounding genomic DNA. The long AT stretches do not occur in the randomized sequence of the human genome. The extremely long AT stretches are much less abundant in the mouse genome. The longest is 612 bp in length and only further six are longer than 300bp.

The longest stretches of GC are much shorter than the longest stretches of AT. Yet they still are much longer than in the randomized sequence. In the human genome, the longest GC tract has 261 bp in length, further eight are longer than 100 bp. In the mouse genome the longest GC tract contains 137 bp and there still is only one longer or equal to 100 bp. The 137 bp GC tract occurs in chromosome 6, the 100 bp GC tract is located in chromosome 20. In the human genome, the 261 bp GC tract is in chromosome 8, of the further 8 longer than 100 GC pairs there are two in chromosome 8 as well, three are in chromosome 2, and one is in chromosome 11, 18 and 7. The tract of 1040 AT pairs occurs in the human chromosome 16, further two equal or longer than 600 bp are located in chromosome 6 and 8. The chromosomes 1, 3 and 15 contain one such long AT tract. In the mouse genome, the AT tract longer than 600 bp is in chromosome 9, two longer than 300 bp in chromosome 6, and one in chromosomes 8, 4, 3 and 2.

DNA adopts double-helical conformations B and A, the latter being induced by dehydration, binding of certain proteins and ions. We continued studies of the B-A transition in DNA using UV light that damages effectively the nitrogenous bases in nucleic acids. This approach takes advantage of the fact that A-form is much less susceptible to the damage caused by UV light than the B-form. In order to monitor the UV light-induced damage at single nucleotide resolution, we introduced the method of primer extension, i. e. a DNA strand synthesis on a DNA template damaged by UV light. The synthesis is stopped before the site of damage to give a population of incompletely synthetized DNA strands whose length distribution can be determined by sequencing electrophoresis. This way one can qualitatively as well as quantitatively evaluate the sites damaged by UV light. We performed parallel experiments using the primer extension as well as restrictase cleavage of the polylinker sequence of the pUC19 plasmid DNA in the course of the B-A transition. We found that there was not only a qualitative but also a quantitative correlation of the primer extension and restrictase data regarding the restrictase inhibition by the damaged DNA and the damage caused by UV light and detected by primer extension in the restrictase recognition sites.
We have taken atomic coordinates of the bases and the C1' atoms of the attached sugars from the DNA crystal structures deposited in the NDB database and calculated all interatomic distances between the neighboring bases along the strand for each step. For example, a GpC step was characterized by 108 distances (12x9 because G and C had 12 and 9 atoms, respectively). The GpC step occurred many times in the NDB database, and the 108 distances could be used to characterize their base stacking similarity using the average value of the differences of the 108 distances. We have used this average value to assess conformational variability of the GpC step in the crystalline B-DNA double helices, A-DNA double helices as well as base stacking geometry differences of the GpC steps between B-DNA and A-DNA. We carried out this analysis for all 16 dinucleotide steps of DNA. The results were plotted in the form of 48 histograms showing the frequency of occurrence of the average distance difference for all 16 steps within B-DNA, within A-DNA and between A-DNA and B-DNA. The histograms document sequence dependence of variability of base stacking within B-DNA and A-DNA as well as the sequence dependent differences of base stacking between B-DNA and A-DNA.

GRANTS:

GA AS CR A1004201

Biophysical properties of (guanin+cytosine) and (adenin+thymine) regions in the DNA molecules of human chromosomes

Principal Investigator: J. Kypr, 2002 - 2006

GA AS CR IAA1004301
Conformational transitions in plasmid DNA
Principal Investigator: K. Nejedlý, 2003 - 2005

GA AS CR K5052113
Genome structure, expression and interactions
Principal Investigator: V. Pačes, IMG AS CR Prague, Co-principal Investigator: J. Kypr, 2001 - 2004

GA CR 301/01/0590
Structural properties and expansion of mononucleotide and dinucleotide microsatellites of the human genome
Principal Investigator: J. Kypr, 2001 - 2003

IGA MH CR NM7634-3/2003
A method development for prediction of pathological expansion of trinucleotide repeats in the human genome
Principal Investigator: J. Kypr, 2003 - 2005

LABORATORY OF MOLECULAR EPIGENETICS (LME)

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	RNDR. MILOSLAVA FOJTOVÁ, CSC.
	RNDR. JAROSLAV FULNEČEK, CSC.
	RNDR. BLAŽENA KOUKALOVÁ, CSC.
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TECHNICAL ASSISTANT:	DANUŠE FRIDRICHOVÁ
UNDERGRADUATE STUDENT:	KATEŘINA KŘÍŽOVÁ

Epigenetic switch between posttranscriptional and transcriptional silencing is correlated with hypermethylation of promoter in a tobacco transgenic locus

In higher eukaryots, genes can be silenced by transcriptional and posttranscriptional mechanisms. The posttranscriptional gene silencing (PTGS) process is characterized by several features, including normal transcriptional activity of the promoter, transcript instability, and ability to degrade homologous RNA, whereas in transcriptional silencing (TGS) the promoter is inactivated and no or little transcripts are produced. Methylation of cytosine residues is associated with both TGS and PTGS; however, the location of methylcytosines within the silenced genes differs for each type of silencing. In TGS, transgenes are frequently methylated in the promoter region, whereas PTGS is correlated with methylation of the transcribed region, particularly at its 3' end.

In the present study we used two tobacco transgenic lines carrying a nptII reporter gene linked to the strong 35S pomotor. The posttranscriptionally silenced locus 1 in the line hemizygous for locus 1 (HeLo1) contains a T-DNA inverted repeat and expression of the residing neomycin phosphotransferase II (nptII) genes was more than 100-fold reduced at the protein level compared to a nonsilenced line hemizygous for locus 2 (HeLo2) bearing a single copy insertion of the T-DNA (Van Houdt et al., 2000). Cytosine methylation of silenced locus 1 was restricted to the 3' end and center part of the transcribed region. The biochemical experiments using hypomethylation drugs 5-azacytidine and dihydroxypropyladenine have failed to induce significant hypomethylation of the sites in a close proximity of the inverted repeat centre (compared to other genomic regions) suggesting the presence of a strong methylation signal within the locus 1 (Kovarik et al. 2000).

Changes in the distribution of methylcytosine residues along a transgene locus of tobacco (*Nicotiana tabacum*) in relation to the type of gene silencing were studied in parental plant leaves, calli, and regenerated plants derived thereof (Fojtova et al. 2003). Expression and epigenetic state of a non silenced HeLo2 line remained stable in cell culture. However, in HeLo1 line carrying a posttranscriptionally silenced

locus 1 with an increasing number of cell cycles DNA methylation changed gradually and methylation was introduced into the promoter. After 24 months of callus in vitro cultivation, an epigenetic variant, designated locus 1E, was obtained in which cytosine methylation of symmetrical (CG and CNG) sites was almost complete within the 5' end of the nptII-transcribed region and the 35S promoter (Table 1).

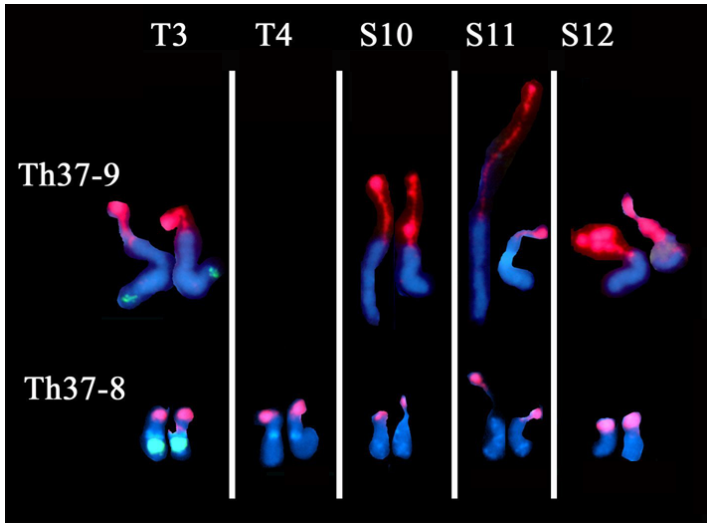
Table 1.: Characteristics of the original and epimutated locus 1 in HeLo1 and HeLo1R5 lines

Locus 1	***Type of silencing***	***Restriction enzyme***	***Methylation context***	***Region***	***Degree of methylation***
Wild type	PTGS	SmaI	Symmetrical, CG	3’ nptII	+++
		BamHI	Nonsymmetrical	3’ nptII	++
		ClaI	Symmetrical, CG	5’ nptII	-
		TaiI	Symmetrical, CG	Promotor 35S	-
		Sau96I	Nonsymmetrical	Promotor 35S	-
		AluI	Symmetrical, CNG	Promotor 35S	-
Epimutated	TGS	SmaI	Symmetrical, CG	3’ nptII	+++
		BamHI	Nonsymmetrical	3’ nptII	(+)
		ClaI	Symmetrical, CG	5’ nptII	+
		TaiI	Symmetrical, CG	Promotor 35S	+++
		Sau96I	Nonsymmetrical	Promotor 35S	+++
		AluI	Symmetrical, CNG	Promotor 35S	+++

Further, methylation of nonsymmetrical sites appeared *de novo* in the promoter whereas this type of methylation was significantly reduced in the 3' end of the transcribed region when compared with parental locus 1.The newly established epigenetic patterns were stably transmitted from calli into regenerated plants and their progeny. The protein and steady state RNA levels remained low in locus 1E whereas with nuclear run-on assays no detectable amounts of primary transcripts were found along the *npt*II gene, indicating that the methylated promoter became inactivated (Table 1). The results suggest that a switch between posttranscriptional and transcriptional gene silencing could be a mechanism leading to irrevocable shut down of gene expression within a finite number of generations.

Rapid evolution of repetitive DNA sequences in synthetic tobacco line

Nicotiana tabacum formed about 6 million years ago is a natural hybrid and polyploid derived from diploid species *Nicotiana sylvestris* (maternal donor of S-genome) and *Nicotiana tomentosiformis* (paternal donor of T-genome) (Murad et al. 2002). Its genome underwent numerous genetic changes including interlocus chromosomal translocations and ribosomal RNA genes (rDNA) gene conversion (Kovarik et al 1996, Lim et al. 2000). On the other parts of genome remained intact (Fulnecek et al. 2002). In order to study early changes associated with allopolyploidy we studied synthetic tobacco line, Th37, 4n (♀*N. sylvestris* x ♂*N. tomentosiformis*). The line has been obtained from the USDA (South Carolina, USA) seedbank and the fourth generation of plants was subjected to extensive genetic analysis (Skalicka et al. 2003). Using genomic in situ hybridisation we have confirmed the allotetraploid character of the line (2n=48). In most plants (85%) we identified novel rDNA units of *N. tomentosiformis*-type containing rearranged subrepeats in intergenic spacer. Their presence was often accompanied by near complete elimination of parental *N. tomenosiformis*-donated units. Fluorescence *in situ* hybridisation (FISH) revealed a novel rDNA locus within the T-genome (on T4 chromosome, Figure 1). The unit structure, number of loci of maternally-donated rDNA remained unchanged. Taken together there is evidence for intralocus but not interlocus gene conversion of rDNA in synthetic tobacco line. Changes in nontranscribed satellites were observed prevalently in the T-genome suggesting that the paternal donor genome might be subjected to rapid evolution. However, it is also possible that decondensed chromosomal loci in interphase e.g. the 35S rDNA are more vulnerable to genetic change. We conclude that repetitive sequences evolved in Th37 line within few generations after allopolyploid nucleus formation.



Fluorescence in situ hybridisation of rDNA luciin Th37 line. Plant Th37_9 contained additive number Of rDNA bd; pbant Th37_8 had an extra bocus on T4 chromosome. Note differentiab level of chromatin condensation at individual 10cl. The probe was the 35S rRNA gene from T. aestivum labelled with Cy3.

GRANTS:

GA CR 521/00/0037
The role of epigenetic factors in regulation of gene expression in higher plants
Principal investigator: A. Kovařík, co-investigator: A. Holý, IOCHB AS CR, Prague, 2001 - 2003

GA CR 204/01/0313
Evolution and mutual interactions between homologous loci in allopolyploid genomes
Principal investigator: R. Matyášek, 2001 - 2003

GA CR 204/03/P104
The structure and expression of ribosomal RNA genes in allotetraploid and their parental genomes
Principal investigator: J. Fulneček, 2003 - 2005

GA AS CR S 5004010
Development of new diagnostic tools in oncology
Principal investigator: S. Kozubek, co-investigator: A. Kovařík, 2000 - 2004

GA CR 521/01/P042
Regulation of posttranscriptional gene silencing in transgenic plants
Principal investigator: M. Fojtová, 2001 - 2003

GA AS CR K5052113

Structure, expression and interaction of genomes
Principal investigator: V. Pačes, IMG AS CR Prague, co-investigator: A. Kovařík, 2001 - 2004

PROGRAM IV

MOLECULAR CYTOLOGY AND CYTOGENETICS

LABORATORY OF MOLECULAR CYTOLOGY AND CYTOMETRY (LMCC)

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	DOC. RNDR. MICHAL KOZUBEK, CSC.
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	RNDR. VLADAN ONDŘEJ, PH.D.
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GRADUATE STUDENTS:	MGR. ING. JANA AMRICHOVÁ
	MGR. MARTIN FALK
	MGR. EVA FALTÝSKOVÁ
	MGR. ANDREA HARNIČÁROVÁ
	MGR. RENATA PASEKOVÁ
UNDERGRADUATE STUDENT:	GABRIELA GALIOVÁ

Nuclear and territorial topography of chromosome telomeres in human lymphocytes

Nuclear and territorial positioning of p- and q- telomeres and centromeres of chromosomes 3, 8, 9, 13 and 19 were studied by repeated fluorescent in situ hybridisation, high-resolution cytometry and three-dimensional image analysis in human blood lymphocytes before and after stimulation. On the basis of these results, we determined the positioning, shape, orientation and polarity of chromosome territories in cell nuclei and changes of these parameters after stimulation and entering into the cell cycle. Mutual distances between telomeres of submetacentric chromosomes were very short, usually shorter than centromere-to-telomere distances (Fig. 1), which means that the chromosome territory is non-randomly folded. Telomeres are in average much nearer to the centre of the cell nucleus than centromeres; q-telomeres were found in average localized more centrally as compared with p-telomeres. Consequently, we showed directly that chromosome territories in the cell nuclei are (i) polar and (ii) partially oriented. Telomeres were found on the opposite side of the territories as compared with the centromeres for all chromosome

territories investigated. The distributions of genetic elements relative to chromosome territories (territorial distributions) can be either narrower

or broader than their nuclear distributions, which reflects the degree of adhesion of an element to the territory or to the nucleus. For example, q-telomere of HSA 19 in G_0-lymphocytes is tightly bound up with the territory (the territorial distribution is much narrower), while p-telomere of HSA 19 in stimulated lymphocytes is tightly bound up with the cell nucleus (the territorial distribution is much broader). We further confirmed that chromosome territories with higher gene density and expression are localized in average more centrally.

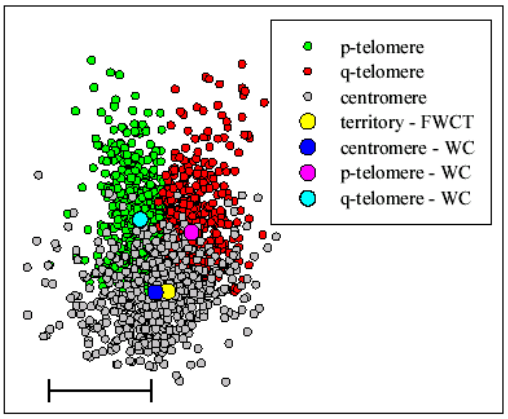

Fig.1.: Structure of interphase chromosome. As a typical example the structure of chromosome 8 in the nucleus of G_0- lymphocytes is shown. The positions of centromeres (gray circles), p-telomeres (red circles) and q-telomeres (green circles) were determined for 275 nuclei in 3D space and placed to the x-y plane in such a way that all chromosomes are superimposed over each other. Genetic loci form clusters which are minimized by a least square fit (the sum of squares of distances between genetic elements and weight centers of the clusters is minimized for each chromosome).

The most central location was observed for HSA 19, most peripheral for HSA 3 in both cell types. Our studies were also focused on the investigation of telomere association phenomenon in the case of homologues and heterologues chromosomes. We found no tethering of heterologous telomeres of HSA 8, 9, and 19. On the contrary, homologous telomeres of HSA 19 (but not in other chromosomes) are

tethered and associated very frequently. The most frequent tethered state arises between p-p telomeres of HSA 19 (about 80,2% of all measured nuclei); the nuclei with both telomeres tethered are also frequent and represent about 40,6 % of all cases. The cases with both telomeres separated show the lowest occurrence (16,2%). In addition, our results confirmed our earlier findings showing non-random and element-specific radial distributions (distributions of centre of the nucleus to element distances) of genetic elements investigated but random angular distributions (distributions of element-centre-element angles) in majority of cases.

Arrangement of chromosome 11 and 22 territories, EWS and FLI-1 genes, and other genetic elements of these chromosomes in human lymphocytes and Ewing sarcoma cells

Chromosomes 11 and 22 are involved in the t(11;22)(q24;q12) translocation responsible for 85% of Ewing sarcomas. This translocation results in fusion of the EWSR1 and FLI1 genes. To contribute to the elucidation of the cause of this translocation, nuclear topography of both the chromosome territories, the EWSR1 and FLI1 genes, and some other genetic elements of these chromosomes was studied in human G_0-lymphocytes and Ewing sarcoma cells.

Spatial arrangement of the investigated genetic elements suggests the existence of some regularities in their higher order structure. It was found that the radial positions of the investigated genetic elements correspond to the positions of their chromosome territories: HSA 11 and its genetic elements (BCL1, FLI1 and centromere) were found, on average, more peripherally in comparison with HSA 22 and investigated elements (BCR, EWSR1, centromere). This radial positioning correlates with a higher gene density of HSA 22 as compared with HSA 11. These results support the evidence of a specific radial location of chromosome territories in cell nuclei, which might be related to certain chromosome characteristics (e.g. gene density, R/G-band content, gene expression).

In Ewing sarcoma cell nuclei, the fusion genes pertaining to both derivative chromosomes 11 and 22 are shifted to the midway position between the native EWSR1 and FLI1 genes. Different location of the fusion genes might be explained by a substitution of a small part of HSA 11 for a larger part of HSA 22 and vice versa. The transfer of a part of HSA 22 with high gene density to HSA 11 causes relocation in the central direction of the translocation neighbourhood of chimeric HSA 11. On the other hand, the translocation neighbourhood of the chimeric HSA 22 is shifted towards the nuclear periphery. This allows to suggest that the mean radial positions of the fusion genes do not depend on the position where the exchange between the

chromosomes occurred, but that they are probably determined by the final structure of the chimeric chromosomes. Comparing results obtained for the EWSR1/FLI1 and ABL1/BCR genes in samples of patients suffering from Ewing sarcoma or chronic myelogenous leukaemia (CML), it can be concluded that different spatial localization of the critical genes might be one of the factors responsible for much lower incidence of Ewing sarcoma in comparison with CML.

In addition to radial distributions, the mutual distances between genetic elements of HSA 11 and 22 in cell nuclei were measured. Monte-Carlo simulation can predict the distributions of element-to-element distances on the assumption of a random element positioning inside nuclear layers at element-specific radial distance. In general, a good agreement between the measured distributions and the theoretical ones was obtained for nearly all the investigated genetic elements in nuclei of human lymphocytes as well as Ewing sarcoma cells suggesting a random distribution of the genetic loci in nuclear layers. However, the EWSR1-EWSR1 (HSA 22) and BCR-BCR (HSA 22) distances were significantly shifted to lower values compared with theoretical prediction. Such observations have also been obtained for distances between the EWSR1 gene and the derivative chromosome 22 fusion gene in nuclei of Ewing sarcoma cells. The higher probability of shorter distances between the EWSR1 (BCR) homologues may be related to their location on the acrocentric HSA 22 (intact or chimeric), which participates in nucleolus formation.

Furthermore, the spatial arrangement of genetic loci (FLI1, BCL1, EWSR1 and BCR genes and centromeres) inside the chromosome 11 and 22 territories has been studied. The results establish no general validity of correlation between the spatial and molecular distance of two loci of the same chromosome territory. After elimination of fluctuations of chromosome territories in nuclear volume, it was found that the genetic elements in most cases adhered to their territories. The investigated genetic elements of HSA 11 were found close to each other relative to the large molecular lengths among them, which indicates a higher degree of chromatin condensation of at least a part of HSA 11 compared with HSA 22. Our results suggest that both the chromosome 11 and 22 territories are not a simple polar structure oriented from the nuclear periphery to the centre of nucleus but that they exhibit some kind of bending in the lateral direction in most cell nuclei.

Grants:

GA CR 301/01/0186
Study of the local control of gene expression using spectral microscopy and image analysis
Principal investigator: S. Kozubek, 2001 - 2003

GA CR 202/01/0197
Ionizing radiation as a tool for the investigation of the chromatin structure in cell nuclei and for the development of new techniques for the ecology and medicine
Principal investigator: S. Kozubek, 2001 - 2003

GA CR 202/02/0804
Chronic myeloid leukemia radiation risk estimation based on BCR -ABL distance in hematopoietic cells
Principal investigator: E. Lukášová, 2002 - 2004

GA CR A1065203
The use of multiple optical tweezers to controlled manipulation and rotation of microobjects. Principal investigator: P. Zemánek, Co-principal investigator: E. Lukášová, 2002 - 2006

GA AS CR B5004102
Nuclear topography of some protooncogenes in human neutrophils and leukemic cells
Principal investigator: E .Bártová, cooperation with FI MU, 2001 - 2003

GA AS CR S5004010
Development of new diagnostic techniques for oncology
Principal investigator: S. Kozubek, 2000 - 2004

GA AS CR K5052113
Structure, expression and interaction of genome
Principal investigator: V. Pačes, ÚMG AS CR Prague, co-investigator: S. Kozubek, 2001 - 2004

GA AS CR IAA5004306
Human genome structure
Principal investigator: S. Kozubek, 2003 - 2008

IGA MH CR NC 6987-3
Epigenetic control of gene expression in malignant diseases
Principal investigator: S. Kozubek, 2002 - 2004

LABORATORY OF PLANT DEVELOPMENTAL GENETICS (LPDG)

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UNDERGRADUATE STUDENTS:	PAVLA HRUŠÁKOVÁ
	MICHAELA MARKOVÁ
	PETRA BULÁNKOVÁ

The dioecious species *Silene latifolia* has a sex determination mechanism based on the active role of the Y chromosome. Interspecific hybrids in the genus *Silene* make it possible to study gene complexes on the Y chromosome. If the function of Y-chromosome-linked genes has been maintained in comparison with its autosomal progenitor, it should be possible to substitute such genes by genes coming from a related hermaphrodite species. This is exactly what we have observed in the inter-specific hybrid *Silene latifolia x S. viscosa*. In the hybrid, anthers developed far beyond the early bilobal stage characteristic of the XX *S. latifolia* female progenitor plants. However, two anther developmental defects were observed. The first is characterised by a developmental arrest of the tapetum, while the second displays precocious endothecium maturation. Both these defects were also found in Y-chromosome deletion mutants of *S. latifolia.* These defects are apparently caused by the absence of Y-chromosome-specific genes. The tapetal phenotype of the hybrid

suggests the presence of a male sterile cytoplasm in *S. latifolia*, together with a restorer gene on the Y chromosome. The endothecial phenotype indicates the existence of an active suppression of male organ development by the female genome, which suggests the existence of Y-specific suppressor of suppressor(s) of anther development. The presented results suggest that the evolution of sex chromosomes in *S. latifolia* probably proceeded according to the following model (Fig. 1): (A) Cytoplasmic male sterility (CMS) as the first step leading to the sex chromosome evolution. (B) Appearance of a fertility restorer (Rf) was followed by (C) the acquisition of a gynoecium suppressing function (GS) and by a loss of recombination between the GS and Rf loci. (D) Male-advantageous sexually antagonistic genes (SAG) recruitment to the proximity of Rf. (E) Low levels of recombination still remained between Rf and SAG. (F) As a consequence, both the male and female fertility decreased. (G) An active suppression of SAG evolved in the recombinant females. (H) Suppression of the male-favourable SAG in males decreased their fitness. (I) Y-specific suppressor(s) of suppressor (SS) or loss of sensitivity to the suppression evolved in the male genome. (J) Translocation of the early stamen-promoting function (SPF) from an autosome to the proto-Y chromosome lead to arrest of anther development in females.

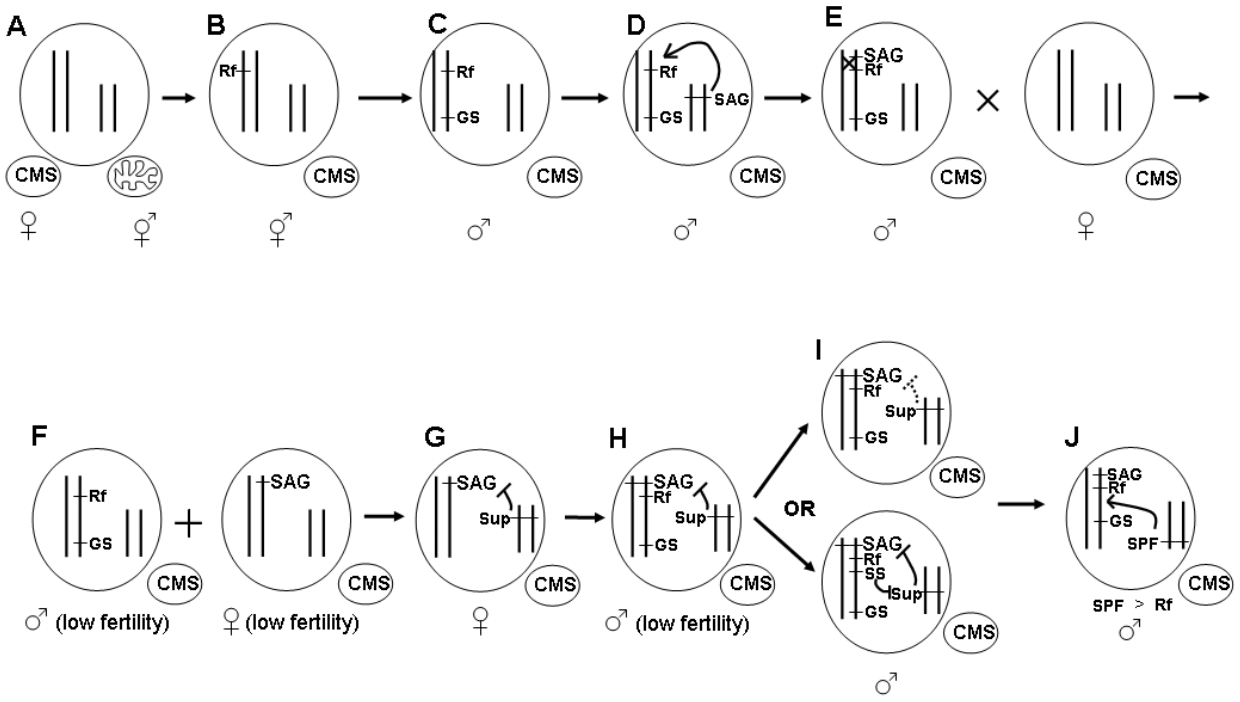

Fig.1. Probable model of the evolution of chromosome Y in Silene latifolia.

It is very hard to distinguish individual arms of the Y chromosome of *Silene latifolia* because it is almost completely metacentric. Classical studies have established that, during meiosis, the X and Y chromosomes pair over a region at the ends of their q arms. We used fluorescence *in situ* hybridization of two molecular markers to demonstrate that this widely accepted model is incorrect. We present a revised vision of the *S. latifolia* sex chromosomes based on the results of these experiments. Contrary to Westergaard's (1946) depiction of the sex chromosomes (Fig. 2), the PAR is located on the p arm of the X chromosome. The establishment of the proper orientation of the pseudoautosomal region is essential for mapping and evolutionary studies.

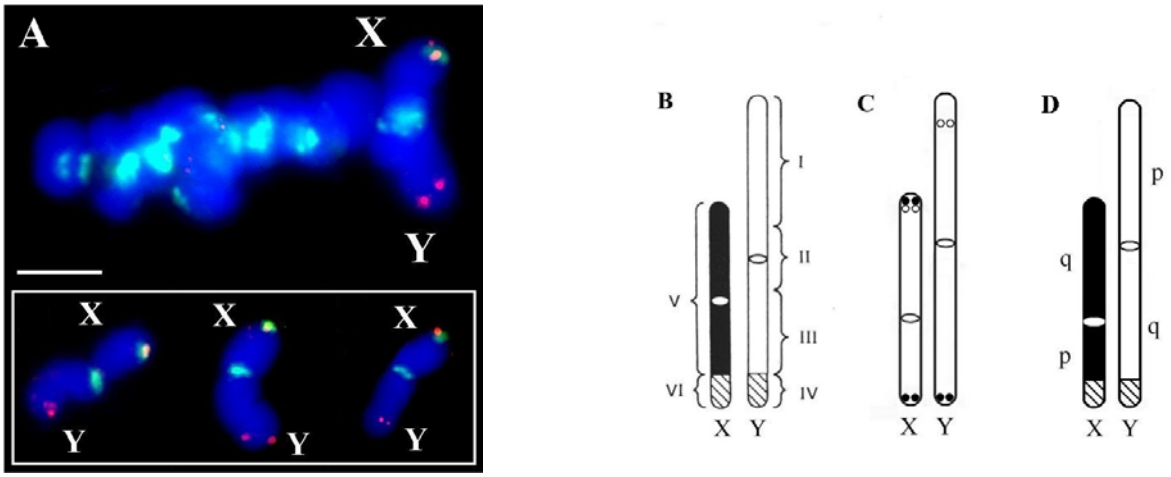

Fig. 2. Results of FISH and schematic drawings of the X and Y sex chromosomes in Silene latifolia. (A) Bicolor FISH using the subtelomeric repetitive sequence, X43.1, and the 18-kb genomic clone, DD44, on S. latifolia meiotic chromosomes. FISH probes are visualized as green (X-43.1) or red (DD44) respectively (when merged the signals look yellowish on the X). Bar represents 10 μm. (B) Classical scheme of the structure of the S. latifolia sex chromosomes as presented by Westergaard (1946). I, II, III - differential parts of the Y chromosome (I - segment containing female suppressor region, II - segment containing genes which initiate anther development, III - segment containing genes which control later stamen development). V - differential part of the X chromosome. Pseudoautosomal regions (IV, VI) are indicated on q arms of both the sex chromosomes. (C) Diagram of FISH hybridization signals on the sex chromosomes for the subtelomeric repeat probe, X-43.1 (●), and the sex-linked genomic probe, DD44 (○). We present a new model (D) of the sex chromosomes in S. latifolia. The PARs are cross-hatched and are present on the p arm of the X and the q arm of the Y. Differential parts of the X (black) and Y (white) are indicated as in (B) model. The relative size and arm ratios are in scale, but the length of the PAR is arbitrary.

We have described a duplicative transfer of a MADS box gene *SlAP3* from autosome onto the Y chromosome in *S. latifolia* (realised in collaboration with Dr. Sachihiro Matsunaga, University of Osaka). This Y chromosome paralog has no X-linked homologs, as was shown by PCR on flow sorted autosomes and X chromosomes. RT-PCR and *in situ* hybridization analysis showed that the autosomal homolog is expressed in developing petals while the Y-linked paralog is much more strongly expressed in male reproductive organs (stamens). The acquisition of autosomal gene by the Y chromosome is an important event in the evolution of plant sex chromosomes.

We have also analysed mutant plants of *Arabidopsis thaliana* (collaboration with Prof. Dorothy Shippen, Texas A&M University) deficient in catalytic subunit of telomerase. During the cultivation of plants after self-pollination gradual loss of telomeres occurred and it was connected with multiple developmental defects, decreased viability and plant sterility. As revealed cytologically, telomere shortening due to telomerase inactivation resulted in fusion of homologous or heterologous chromosomes, leading to their successive breakage during anaphase movement, followed by fusion of broken ends in the next cell cycle, i.e. the breakage-fusion-bridge (BFB) cycle. Using fluorescence *in situ* hybridization with rDNA and chromosome-specific BAC probes we demonstrated a participation of chromosomes 2 and 4 in the formation of anaphase bridges. Both homologous and non-homologous chromosomes formed transient anaphase bridges whose breakage and unequal separation led to genome rearrangement, including non-reciprocal translocations and aneuploidy (Fig. 3). rDNA loci at the ends of chromosomes 2 and 4 were observed in chromosome bridges at a frequency approximately 10-times higher than expected in the case of random fusion events which is a result of functional association of rDNA repeats at nucleoli. We also describe increased variation in the number of nucleoli in some interphase cells with supernumerary rDNA FISH signals. These data indicate that dysfunctional telomeres in *Arabidopsis* lead to massive genome instability, which is induced by multiple rounds of the breakage-fusion bridge mechanism.

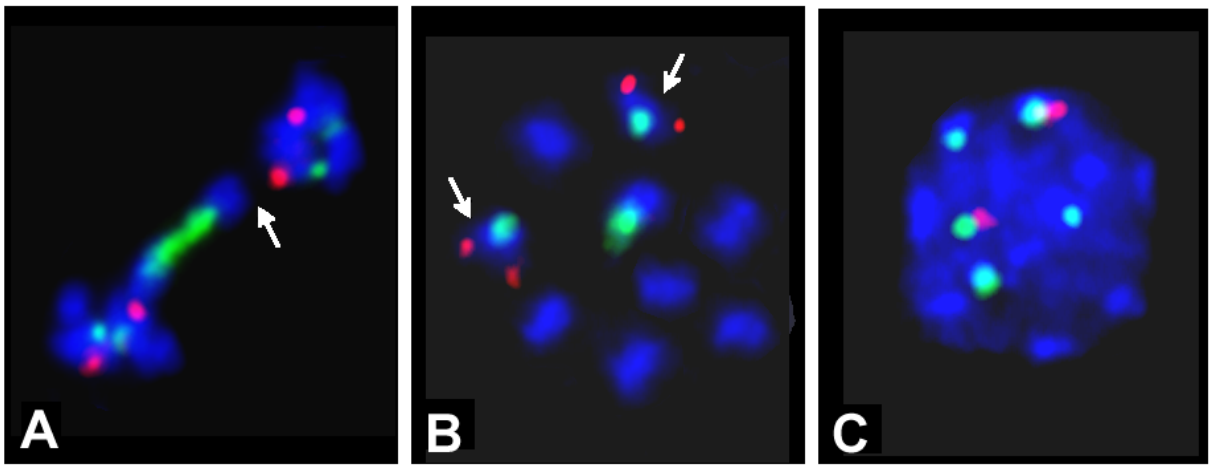

Fig. 3. FISH on nuclei of A. thaliana telomerase-deficient plants. Green signals – rDNA probe, red signals – chromosome 4 specific probe. Nuclei counterstained with DAPI (blue). (A) Rupture (arrow) of anaphase bridge consisting of rDNA loci from chromosomes 2 leading to unequal distribution rDNA to daughter nuclei. (B) Aneupliod metaphase lacking chromosome 2. Chromosomes 4 are indicated by arrow. (C) Interphase nucleus displaying additional FISH rDNA signal.

GRANTS:

GA CR 204/02/0417
Structure and function of sex chromosomes of *Silene latifolia*
Principal investigator: B. Vyskot, 2002 - 2004

GA AS CR A6004304
Epigenetic consequences of telomere dysfunction in *Arabidopsis thaliana*
Principal investigator: B. Vyskot, 2003 - 2006

GA AS CR K5052113
Structure, expression and interaction of genome
Principal investigator: V. Pačes, ÚMG AS CR Prague, co-investigator: B. Vyskot, 2001 - 2004

GA CR 522/03/0354
Cytogenetic study of organization of plant nucleus
Principal investigator: J. Široký, 2003 - 2005

GA CR 522/02/1485
Histological and functional analysis of gene complexes of the Y chromosome in *Silene latifolia*
Principal investigator: B. Janoušek, 2002 - 2004

GA CR 521/02/0427
Construction and analysis of BAC library of *Silene latifolia*
Principal investigator: E. Kejnovský, 2002 - 2004

LABORATORY OF MOLECULAR ANALYSIS OF PLANT DEVELOPMENT (LMAPD)

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	MGR. JAN ZOUHAR, DR.
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	MGR. JAN HEJÁTKO
	MGR. JAKUB HORÁK
	MGR. MARKÉTA ŠÁMALOVÁ
	MGR. PETRA BORKOVCOVÁ
	MGR. HANA BUBENÍČKOVÁ
	MGR. ALENA REKOVÁ
	MGR. MICHAL SLANÝ
	MGR. PŘEMYSL SOUČEK
UNDERGRADUATE STUDENTS:	PETR KLÍMA
	PAVEL MAZURA

Biological function of a putative cytokinin receptor CKI1

Previously, we have found that a two-component sensor histidine kinase CKI1, originally implicated in cytokinin perception, is required for completion of megagametogenesis in *Arabidopsis*. However, *CKI1* expression analysis suggests CKI1 function in sporophytic tissues, too. To elucidate the potential role of CKI1 in sporophytic tissues, the use of antisense RNA and/or posttranscriptional gene silencing (RNA interference, RNAi) approaches are necessary, as the mutant *cki1* alleles cannot be obtained in the homozygous state. To prepare corresponding plant transformation vectors, *CKI1* specific sequences in the antisense and sense orientations were linked with a fragment of *GUS* gene and the construct was placed, in two separate vectors, under the control of a constitutive, CaMV35S, and

a regulatable, pOp, promoter. Transgenic Arabidopsis lines were derived by Agrobacterium vacuum infiltration. Efficiency of *CKI1* silencing is analyzed in transgenic lines selected after transformation.

Functional architecture of an active site in a maize β*-glucosidase Zm-p60.1*

The project aims to deepen our understanding of molecular determination of aglycone specificity in β-glucosidases. Previously, we have found at least two distinct modes of molecular determination of preferential affinity for aromatic aglycones in two β-glucosidase sub-families. We are making use of the gained information to re-construct, in the scaffold of a representative of the first sub-family, Zm-p60.1, an active site of a representative of the second sub-family. In addition to the complete re-construction, we have prepared another three intermediate chimeric proteins by stepwise increasing the number of amino acid residue substitutions leading from the original active site to the fully re-constructed one. This should allow us to assess contribution of individual amino acid residues and their defined clusters to functional architecture of the respective active sites. The chimeric ORFs are expressed in a bacterial expression system, and biophysical properties of the chimeric proteins are being investigated.

GRANTS:

GA CR 203/02/0865
Functional architecture of an active site in a maize β-glucosidase
Principal investigator: B. Brzobohatý, 2002 - 2004

IGA MEdYS CR, LN00A081, 2000 - 2004
Signalling pathways in plants
Principal investigator: B. Brzobohatý, 2002 - 2004

GA AS CR K5052113
Structure, expression and interaction of genome
Principal investigator: V. Pačes, ÚMG AS CR Prague, co-investigator: B. Brzobohatý, 2001 - 2004

PROGRAM V

KINETCS OF CELL POPULATIONS

LABORATORY OF CYTOKINETICS (LC)

HEAD:	DOC. RNDR. ALOIS KOZUBÍK, CSC.
SCIENTISTS:	DOC. RNDR. JIŘINA HOFMANOVÁ, CSC.
	RNDR. JAN VONDRÁČEK, PH.D.
	MGR. MARTINA KOVAŘÍKOVÁ, PH.D.
	MGR. KAREL SOUČEK, PH.D.
	MGR. ALENA VACULOVÁ, PH.D.
	MGR. KATEŘINA CHRAMOSTOVÁ, PH.D.
RESEARCH FELLOWS:	RNDR. JIŘINA HOLÁ
	MGR. JAROMÍRA NETÍKOVÁ
TECHNICAL ASSISTANT:	MARTINA URBÁNKOVÁ
GRADUATED STUDENTS:	MGR. ZDENĚK ANDRYSÍK
	MGR. JIŘÍ ŠTIKA
	MGR. LENKA ŠINDLEROVÁ
	ING. VIKTOR HORVÁTH
UNDERGRADUATE STUDENTS:	LENKA UMANNOVÁ
	LENKA STIXOVÁ
	HANA NOVOTNÁ
	ZUZANA SCHMIDTOVÁ

The research in the Laboratory of Cytokinetics is focused to understanding of the role of lipid cell membrane components and their derivatives (especially arachidonic acid and its metabolites) in the effects of environmental factors (nutritional lipids and xenobiotics – polutants and drugs) affecting cell signalling. The interaction with specific endogenous regulators of proliferation, differentiation and apoptosis in cancer as well as non-cancerous cell populations is investigated. Information about deregulation and modulation of specific signalling mechanisms regulating cytokinetics and intercellular communication are applied in the field of ecotoxicology and cancer prevention and therapy.

The role of transforming growth factor - β1 (TGF-β1) during differentiation and apoptosis of myeloid cells

The interaction between retinoids and TGF-β1 involved in regulation of proliferation, differentiation and apoptosis is not still fully understood. Our new studies showed that inhibition of proliferation, potentiation of differentiation, and the shift towards monocyte-like phenotype of myeloid HL-60 cells by combined treatment with TGF-β1 and all-*trans* retinoic acid (ATRA) is accompanied by inhibition of ATRA-induced apoptosis. This effect was preceded by G0/G1 arrest of the cell cycle linked with pRb protein dephosphorylation and an increased level of $p21^{waf1,\ cip1}$ (but not p27) protein, an inhibitor of cyclin-dependent kinases. Inhibition of ATRA-induced apoptosis by TGF-β1 was associated with an increased level of Mcl-1 protein, an antiapoptotic Bcl-2 family member, but not with inhibition of mitochondrial membrane depolarization. Levels of other Bcl-2 family proteins (Bcl-2, Bcl-X_L, Bad, Bak, Bax) were unaffected by simultaneous ATRA and TGF-β1 treatment, when compared to ATRA alone. Upregulation of c-$FLIP_L$ protein, an inhibitor of apoptosis induced by tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) might correspond with inhibition of ATRA-induced (and autocrine TRAIL-mediated) caspase-8 activation and apoptosis. The obtained results suggest that apoptosis inhibition associated with proliferation block and enhanced differentiation could depend on modulation of the TRAIL apoptotic pathway and regulation of the Mcl-1 protein level. In summary, we demonstrate that the balance of processes leading to regulation of proliferation and/or maturation of myeloid cells can modulate cell sensitivity to apoptosis-inducing stimuli.

The effects of TNF family apoptosis inductors on colon epithelial cells

The differences in the response of human normal fetal colon FHC and adenocarcinoma HT-29 cell lines to three endogenous apoptotic inducers TNF-α, anti-Fas (CH11) and TRAIL were investigated. Generally, cancer cells were more sensitive to the effects of these agents. After 24 h TNF-α blocked HT-29 cells in S-phase decreasing HT-29 cell growth but did not induce apoptosis. Similar effects were observed after treatment with TRAIL which in addition to that induced apoptosis identically with CH11 (increased % of floating cells, subdiploid G0/G1 population, decreased mitochondrial potential-MMP, activation of caspase-3, cleavage of PARP, and morphological nuclear changes).

We demonstrated that ethanol acts as a potent agent sensitizing the colon cancer cells to the TRAIL-induced apoptosis. TRAIL alone induced only partial effects on caspase activation, PARP and Bid cleavage, and decrease of MMP after 4 h of treatment. This was accompanied by an increase in number of floating cells and cells with apoptotic nuclear morphology, without significant changes in cell viability. A strong

upregulation of Mcl-1 protein was demonstrated, suggesting its possible role in cell resistance to TRAIL-induced apoptosis. Co-treatment of cells with ethanol significantly amplificated the apoptotic signal at the level of mitochondria (decreased MMP, Bid cleavage, caspase-9 activation) as well as increased caspase-8 and -3 activation, PARP cleavage and caused complete disappearance of Mcl-1 protein. Significant increase of number of both floating cells and cells with apoptotic nuclear morphology, accompanied by a strong decrease of cell viability was detected. No involvement of reactive oxygen species -ROS, non-caspase proteases (calpain I) or $FLIP_L$ was proved.

The study of detail mechanisms of supression of differentiation and potentiation of apoptosis in cancer HT-29 and normal FHC colon epithelial cells during interaction of TNF-α with sodium butyrate (NaBt) continued. It was shown that these effects are not associated with expression of AP-1, NF-κB nor PPAR-γ transcription factors. The changes of the activity of these factors after combined treatment of cell with TNF-α and NaBt are detected using stable transfectants involving luciferase gene with binding site for appropriate factor prepared in our laboratory. Using various inhibitors of AA metabolism it was shown that these agents (together with TNF-α and NaBt) further deepened the effects observed, i.e. decrease differentiation (in cancer HT-29 cells) or potentiate apoptosis (in normal FHC cells)

The effects of cytostatics

Cisplatin (*cis*-diamminedichloroplatinum(II), *cis*-DDP) is a chemotherapeutic agent widely used in the therapy of a variety types of cancer, but acquired resistance is a frequent problem in application of this drug. New derivatives of *cis*-DDP are synthetized to find substances able to overcome this problem, e.g. by an exchange of the ligands bound to the platinum atom. One of these compounds, LA-12, was used in our study using ovarian cancer cell lines A2780 (parental line sensitive to *cis*-DDP) and A2780cis (line with acquired resistance to *cis*-DDP).

Concentrations of LA-12 relevant to IC_{50} and IC_{90} are 6-times (parental line) and 18-times (resistant line) lower than concentrations of *cis*-DDP. Treatment of the cells with LA-12 (IC_{90}) for 72 h increased the amount of floating and apoptotic A2780cis but not A2780 cells in comparison with *cis*-DDP. In parental cell line A2780, *cis*-DDP (IC_{90}) caused an increase in number of the cells in S-phase, while LA-12 (IC_{90}) in G2/M-phase of the cell cycle. One of the suggested mechanisms of the action of LA-12 could be an interference with the cell cycle regulation. It may be concluded that LA-12 is effective in considerable lower concentrations than *cis*-DDP in ovarian cancer cell lines A2780 and A2780cis and overcomes resistance to *cis*-DDP .

Evaluation of cell morphology using fluorescence microscopy showed that the type of cell death after LA-12 treatment is rather necrosis than apoptosis. This was confirmed also by the lack of poly-ADP-ribose polymerase (PARP) cleavage and DNA fragmentation detected by electrophoretic methods. Detection of proteins from Bcl-2 family showed that cell lines studied do not expressed Bcl-2 protein. On the other hand, time-dependent increased expression of p53 implies participation of this protein in the mechanisms of LA-12 effects.

The results achieved in ecotoxicology

Using two experimental models, we have studied potential nongenotoxic modes of action of polycyclic aromatic hydrocarbons (PAHs) and heterocyclic aromatic compounds (dinaphthofurans – DNFs), as well as some other groups of aromatic pollutants. It has been found that some PAHs, such as benz[a]anthracene, benzo[a]pyrene and fluoranthene, could stimulate proliferation of human breast carcinoma MCF-7 cells. Moreover, it has been shown that the observed induction of cell proliferation is probably associated with activation of estrogen receptor-α (ER). Our results seem to suggest that this type of ER modulation could play a role in deregulation of cell proliferation and in carcinogenic effects of PAHs. Additionally, it has been found that the effects of PAHs on cell proliferation can be modified also by their genotoxic effects that lead to activation of protective mechanisms, such as accumulation and activation of p53 tumor suppressor.

Furthermore, we have investigated proliferative effects of PAHs and DNFs on rat liver epithelial „stem-like“ cells (WB-F344 cell line), which might be associated with activation of aryl hydrocarbon receptor (AhR). It has been shown that some PAHs (and DNFs), known as AhR ligands can both potentiate cell proliferation and induce cytochrome P450 1A activity, which confirms a presence of functional AhR module in this cellular model. Due to the fact, that effects of PAHs are dependent also on p53 activation associated with cell cycle progress inhibition and induction of cell death, we have further studied potential role of MAP kinases both in cell proliferation and cell death induced by PAHs. Using specific inhibitors and detection of MAP kinase phosphorylation, it has been found that activation of ERK1 and 2 kinases were not involved in the observed proliferative activity. Moreover, it has been shown that cell proliferation is not associated with direct proliferative effects of PAHs, but it is a consequence of disruption of contact inhibition in confluent cell population. On the other hand, it has been found that strongly mutagenic PAHs induce phosphorylation of ERK1 and 2, as well as phosphorylation of p38 kinase. A specific inhibitor of ERK1 and 2 activation has partially abolished induction of programmed cell death by strong mutagens. The present results could contribute to understanding of regulatory mechanisms that might be involved in epithelial cell carcinogenesis. This knowledge

can help to better describe the mechanisms involved in carcinogenic effects of PAHs, as well as other aromatic environmental contaminants.

The results achieved in area of applied research

i) Based on the large bibliographic search perspective direction of production of parenteral lipid emulsions with regard to application of fish oil (rich in n-3 PUFAs) and antioxidants (alpha tocopherol) was detected.

ii) The in vitro effects of four lipid emulsions manufactured by Infusia Hořátev, a. s. (Nutralipids and Deltalipids enriched with alpha tocopherol) on cancer HT-29 and normal FHC colon epithelial cells were investigated. The changes in fatty acid content in cellular lipids (decreased n-3/n-6 PUFA ratio) after treatment of cells with emulsions were accompanied particularly by enhanced ROS production and lipid peroxidation. Both effects were supressed by antioxidant Trolox (an analogue of alpha tocopherol). FHC cells responded more sensitively then HT-29 cells, which can be caused by different oxidative metabolism of normal and cancer cells.

GRANTS:

GA AS CR S5004009
Alternative therapeutic strategies in oncology
Principal investigator: A. Kozubík, 2000 - 2004

GA CR 305/01/0418
Cellular and molecular pharmacology of platinum and ruthenium anticancer drugs
Principal investigator: A. Kozubík, 2001 - 2003

GA CR 525/01/0419
Dietary lipid components in the regulation of cytokinetics of colonic epithelium
Principal investigator: J. Hofmanová, 2001 - 2003

GA CR 525/03/1527
Chemical identification and in vitro screening of toxicity of aromatic contaminants in agricultural production environment
Principal investigator: M. Machala, VÚVeL Brno, co-investigator: J. Vondráček, 2003 - 2005

GA CR 524/03/0766
Modulation of proliferation, differentiation and apoptosis of hemopoietic cells – interactions of cytokines, drugs and lipid nutrition compounds
Principal investigator: A. Kozubík, 2003 - 2005

MPO CR - project Consorcia FD-K/033
Development of parenteral lipid emulsion and technical solution of its application
Principal investigator: INFUSIA a. s., Hořátev
Co-investigators: MedF UK, Hradec Králové; IBP: A. Kozubík, 2001 - 2003

GA CR 525/01/D076
Activation of MAP protein kinase pathways by polycyclic aromatic hydrocarbons in vitro - a potential nongenotoxic mechanism underlying the effects of environmental contaminants
Principal investigator: J. Vondráček, 2001 - 2003, supervisor: A. Kozubík

GA CR 524/02/P051/A
The interaction of cytokine TNF-α with butyrate during differentiation and apoptosis of colon epithelial cells
Principal investigator: M. Kovaříková, 2002 - 2004, supervisor: J. Hofmanová

GA AS CR P105/01/28
Dynamics of processes in living and non-living matter - multifunctional equipment for fluorimetry, photometry and luminometry
Principal investigator: K. Ulbrich, IMCH AS CR Prague, co-investigator: A. Kozubík, 2001 - 2003

GA AS CR K5011112
Molecular and cellular basis of severe disorders
Principal investigator: P. Mareš, IPH AS CR Prague, co-investigator: A. Kozubík, 2001 - 2004

LABORATORY OF EXPERIMENTAL HEMATOLOGY (LEH)

HEAD:	MUDR. MICHAL HOFER, CSC.
SCIENTISTS:	RNDR. ZUZANA HOFEROVÁ, CSC.
	PROF. MUDR. MILAN POSPÍŠIL, DRSC.
	MUDR. ANTONÍN VACEK, CSC.
	MGR. LENKA WEITEROVÁ, PH.D.
RESEARCH FELLOWS:	RNDR. JIŘINA HOLÁ
	MGR. JAROMÍRA NETÍKOVÁ
TECHNICAL ASSISTANT:	VĚRA REICHMANNOVÁ

In 2003, the research was aimed on more detailed evaluation of mechanisms through which pharmacologically induced elevation of extracellular adenosine acts on hematopoietic and tumor cell populations. In experiments employing *in vivo* and *in vitro* techniques, effects of selected synthetic agonists of adenosine receptors, more or less specific for individual receptor subtypes were tested.

Experiments in which effects of non-selective synthetic agonist of adenosine receptors 5'-(N-ethylcarboxamido)adenosine (NECA) and agonists specific for receptor subtypes A_1 (N^6-cyclopentyladenosine, CPA), A_{2A} (2-p (carboxyethyl)-phenethylamino -5'-N-ethylcarboxamidoadenosine, CGS 21680) and A_3 (1-deoxy-1-(6-[([3-iodophenyl]methyl)-amino]-9H-purin-9-yl)-N-methyl-β-D-ribofuranoamide, IB-MECA) on hematopoiesis were evaluated. The results of these experiments have revealed that especially activation of the A_3 receptor subtype is responsible for stimulation of proliferation of hematopoietic progenitor cells for granulocytes and macrophages (GM-CFC) and erythrocytes (BFU-E). In *in vitro* experiments on fibrosarcoma G:5:113 cell line, another feature of IB-MECA, i.e. of a selective inhibitor of the A_3 receptor subtype, namely that of its ability to suppress the growth of the above tumor cell line has been shown. These findings give more precision to our knowledge of processes through which the effects of extracellular adenosine on various cells are mediated. The opposite effects of the agonist of the A_3 receptor subtype on hematopoietic (stimulation of proliferation) and tumor (inhibition of

proliferation) cell populations are especially of interest. These results may be exploited in applied research directed to clinical practice.

GRANTS:

GA AS CR K5011112
Molecular and cellular basis of severe disorders
Principal investigator: P. Mareš, IPH AS CR Prague, co-investigator: M. Hofer, 2001 - 2004

GA CR 305/02/0423
The effects of adenosine analogs on hematopoiesis
Principal investigator: M. Hofer, 2002 - 2004

LABORATORY OF FREE RADICAL PATHOPHYSIOLOGY (LFRP)

HEAD:	RNDR. ANTONÍN LOJEK, CSC.
SCIENTISTS:	RNDR. MILAN ČÍŽ, PH.D.
	RNDR. LUKÁŠ KUBALA, PH.D.
RESEARCH FELLOW:	ING. RADKA BUŇKOVÁ
	MGR MARTINA PAVELKOVÁ
TECHNICAL ASSISTANTS:	BLANKA PANÁKOVÁ
	LENKA VYSTRČILOVÁ
GRADUATE STUDENTS:	MVDR. IVANA PAPEŽÍKOVÁ
	MGR. DANIELA KOMRSKOVÁ
	MGR. LUCIE GALLOVÁ
UNDERGRADUATE STUDENTS:	EVA PRACHAŘOVÁ
	JANA KRÁLOVÁ
	ANETA MORAVCOVÁ
	LUCIE GOJOVÁ
	JANA HAZDROVÁ

The effects of platelets and their mediators on respiratory burst of phagocytes were studied. Platelets, added to neutrophils in the physiological cell ratio 50:1, decreased bacterial polypeptide FMLP-stimulated, phagocyte-derived release of reactive oxygen species by 56% as measured by chemiluminescence. Platelet inhibition of chemiluminescence rose in the presence of chloroquine, which was assumed to be mediated by serotonin liberated from platelets by the action of chloroquine. The following facts supported this hypothesis: (i) chloroquine alone did not affect FMLP-stimulated neutrophils, (ii) it actively liberated serotonin from platelets, and (iii) serotonin was found to be able to reduce chemiluminescence of neutrophils, chemiluminescence of superoxide anion, hydroxyl radical as well as of hydrogen peroxide. The presented results indicated the ability of unstimulated platelets to inhibit neutrophil chemiluminescence by a serotonin independent mechanism as well as the potency of the serotonin-liberating drug chloroquine to enhance this inhibition.

The immunomodulatory effect of hyaluronic acid (HA), which represents the most important glycosaminoglycan in extracellular matrix, was investigated. Since the molecular weight of HA has a remarkable impact on its effect on cells of the immune system, four batches of HA (1540kDa, 740kDa, 480kDa, 390kDa) were tested. All batches induced only mild changes in the production of inflammatory cytokines IL-6, IL-8, IL-10 and TNF-α by blood leukocytes. The expression of CD25 and CD69 on lymphocytes was not changed. On the other hand, HA activated blood phagocytes as was demonstrated by modified expression of surface molecules on polymorphonuclear leukocytes and monocytes (increase in CD11b and CD15, decrease in CD62L). HA also potentiated the metabolic activity of phagocytes induced with bacterial polypeptide FMLP.

Behaviour of homocysteine in an *in-vivo* ischemia/reperfusion model of small intestine was studied. Plasma homocysteine concentration, lipid peroxidation and total peroxyl radical-trapping antioxidant parameter (TRAP) were measured in rats divided into three groups (control group, sham operated group, ischemia/reperfusion group). A significant increase in homocysteine concentration was obtained together with that in lipid peroxidation and TRAP in the ischemia/reperfusion group. The results obtained indicate that plasma homocysteine concentration is enhanced in response to an experimental condition that induces an oxidative stress. The results support the hypothesis that homocysteine can play a protective role against vascular stress.

The luminol-enhanced chemiluminescence method was used to investigate the antioxidative activity of N-(alkoxyphenyl)-2-(2-oxo-1-aza-1-cykloalkyl) acetamides (potential cognitive enhancers) and stobadine acylderivatives. The effect of tested compounds on the production of reactive oxygen species by activated leukocytes was studied *in vitro*. Furthermore, the total radical-trapping antioxidant parameter of tested compounds was evaluated as the peroxyl radical-trapping capacity and their scavenging effect on the superoxide anion and hydroxyl radical were studied. The antioxidative properties of the tested substances were compared with that of stobadine dihydrochloride. Only stobadine and its butyrylderivative have been demonstrated to possess free radical scavenging activity in all systems. Cinnamoylstobadine inhibited only the leukocyte chemiluminescence activity. The potential cognitive enhancers did not show any antioxidant activity.

The contents of the main biochemical compounds and TRAP of various olive oils were compared. A very high correlation between total phenols and antioxidant capacity in studied oils was found. Furthermore, the effect of olive oils on lipid metabolism and total antioxidant activity was investigated in Wistar rats adapted to cholesterol-containing and cholesterol-free diets. Plasma lipids and TRAP, as well as other parameters, were measured. Significant hypocholesterolemic and antioxidant

effects were registered mainly in rats fed cholesterol-containing diets supplemented with olive oils. In conclusion, olive oils positively affect plasma lipid metabolism in rats. These positive properties are attributed mostly to the phenolic compounds of the studied oils.

GRANTS:

GA CR 524/01/1219
Understanding and modulation of the antioxidative defence mechanisms in oxidative stress
Principal investigator: M. Číž, 2001 - 2003

GA CR 524/02/0395
The influence of hyaluronic acid on the functions and interactions of leukocytes and epithelial cells under physiological and inflammatory conditions
Principal investigator: A. Lojek, 2002 - 2004

GA AS CR B6004204
Antioxidative properties of flavonoids with respect to the oxidative burst of phagocytes and cooperation between phagocytes and endothelial cells
Principal investigator: M. Číž, 2002 - 2004

GA AS CR K5011112
Molecular and cellular basis of severe disorders
Principal investigator: P. Mareš, IPH AS CR Prague, co-investigator: A. Lojek, 2001 - 2004

RESEARCH AND TECHNOLOGICAL CENTRES

BIOMOLECULAR CENTRE

COORDINATOR:	MASARYK UNIVERSITY BRNO
PARTICIPANT:	INSTITUTE OF BIOPHYSICS BRNO
HEAD IN THE IBP AS CR:	DOC. RNDR. JIŘÍ ŠPONER, DRSC.

Using molecular-dynamic and thermodynamic methods the analysis of kinetics of intermediary states in the forming of guanine quadruplex (G-DNA) was performed. In this manner explicit inclusion of ions in the channel of the quadruplex was possible. As a result a model allowing quantitative reconstruction of the way of formation of the G-DNA stem could be obtained.

We also performed extensive simulations of the „kissing“ dimmer DIS of the initiation sequence of the virus HIV-1 and the H3 DID retrovirus of the Moloney murine leukemia. We found that kissing complexes are stabilized by the structural pocket, mainly occupied by divalent cations.

SIGNALLING PATHWAYS IN PLANTS

COORDINATOR:	INSTITUTE OF EXPERIMENTAL BOTANY AS CR, PRAGUE
PARTICIPANT:	INSTITUTE OF BIOPHYSICS BRNO
HEAD IN THE IBP AS CR:	RNDR. BŘETISLAV BZOBOHATÝ, CSC.

We isolated and characterized insertion mutations in the gene coding the response regulator AAR21 in *Arabidipsis thaliana*.

CENTRE OF INFORMATION TECHNOLOGIES (LCIS)

HEAD: RNDR. JOSEF JURSA, CSC.

TECHNICIAN: LUKÁŠ POSÁDKA

Standard services of the laboratory:
Operation, servicing and development of the IBP local area network (LAN)
Operation of the connection of the IBP LAN to Brno Academic Computer Network (BACN) and to the Internet
Cary on e-mail server
Cary on www server of the IBP (http://www.ibp.cz) including data updating
Current maintenance and development of computer technique (hardware and software), utilized by all projects solved at the IBP (servers, graphic workstations and simple PCs with Internet access), which is working under UNIX, MS Windows NT/2000/XP and MS Windows 95/98/ME operating systems.
Consulting and guidance services for individual projects. (Expert help - in a limited amount - with solving problems connected with computer technique and computer network.)
Operation and servicing of a ICCBnet (International Center for Cooperation in Bioinformatics network) national node of the Czech Republic - http://ICCBnet.ibp.cz
Mirroring of the Protein Database (PDB) accessible through the Internet
Sequence databases and accompanying software - Wisconsin GCG package - accessible to users from Academy of Sciences and universities in the Czech Republic
Operation and servicing of a library server used by Academy of Sciences in Brno region

In the 2003 there was extended computer network of the IBP to new built laboratories.

Main attention was devoted to security. There was installed firewall on servers and on a router connecting IBP LAN to the BACN and to the Internet. New e-mail system was built and now all e-mail is monitored at the server by virus scanner, dangerous attachments are renamed, so that they cannot be run automatically on PC without user knowledge. In addition a system for limitation of un-requested e-mail (spam) was installed.

In the end of the year there was twice extended address space of the IBP LAN (from 195.178.68.1-195.178.68.254 to 195.178.68.1-195.178.69.254). Then the IP addresses where redistributed.

III. PUBLISHED REPORTS

A. PAPERS PUBLISHED IN JOURNALS AND MONOGRAPHS

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Biotechniques, 35, 2003, 912-914

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In: Proceedings and Program, p. 296

Vařecha, M., Amrichová, J., Ondřej, V., Lukášová, E., Kozubek, S., Kozubek, M.:
Fluorescenční in vivo techniky v buněčné biologii
Symposium teoretické a aplikované biofyziky, České Budějovice, 18. – 20. 9. 2003
In: Program a souhrny sdělení, p. 54

Vařecha, M., Jabůrek M., Dvořák L., Ježek P., Pauček P., Garlid K. D., Kozubek S., Kozubek M.:
Structural and functional characterization of uncoupling proteins UCP1, UCP2, and UCP3
Second Workshop on Biophysics of the Genome, Hlohovec, 2. – 4. 4. 2003
Proceedings of the Conference at Hlohovec, p. 74-81
In: Scientific Programme and Book of Abstracts, p. 46

Vařecha, M., Kozubek, M., Kozubek, S., Zemánek, P.:
Mikromanipulace v buněčném mikrosvětě
Analytická cytometrie II., Brno, 11. – 14. 5. 2003
In: Sborník abstrakt, p. 66-67

Vetterl, V.:

Electromagnetic properties of nucleic acids

University of Joensuu, Department of Physics, Joensuu, Finland, 16. – 18. 7. 2003

Vetterl, V., Hasoň, S., Strašák, L.:

Electrochemical impedance spectroscopy of nucleic acids

Symposium teoretické a aplikované biofyziky, České Budějovice, 18. – 20. 9. 2003

In: Program a souhrny sdělení, p. 56

Vetterl, V., Hasoň, S. ,Strašák, L.:

Electrochemical spectroscopy of nucleic acids and self-assembled layers of nucleosides

54th Annual Meeting of the International Society of Electrochemistry – The Role of Electrochemistry in the Sustained Development of Modern Societies, Sao Pedro, Brazil, 31. 8. – 5. 9. 2003

In: Book of Abstracts, p. 91

Vetterl, V., Jelen, F., Hasoň, S.:

Interactions of nucleic acids at charged interfaces

4th European Biophysics Congress, Alicante, Spain, 5. – 9. 7. 2003

In: Eur. Biophys. J., 32, 2003, p. 228

Víglaský, V.:

DNA-MSC complex study – Bending or unwinding?

MARCY Meeting, Warwick, U.K., 5. – 6. 9. 2003

Vojtíšková, M., Stehlíková, K., Sedlářová, I., Brabec, V.:

Exploitation of a cell-free rapid translation system (RTS) for the preparation of recombinant XPA proteins

XVIIth Biological Days. Memory in Living Systems, Brno, 19. – 20. 11. 2003

In: XVIIth Biological Days. Memory in Living Systems, p. 37-38

Vondráček, J., Andrysík, Z., Chramostová, K., Vojtěšek, B., Souček, K., Kozubík, A., Machala, M.:

AhR-activating polycyclic aromatic hydrocarbons induce a release from contact inhibition or apoptosis in rat liver epithelial cell line

41st Congress of the European Societies of Toxicology EUROTOX 2003 (Science for Safety), Florence, Italy, 28. 9. – 1. 10. 2003

In: Toxicol. Lett., 144 (Suppl. 1), 2003, p. s121

Vondráček, J., Chramostová, K., Plíšková, M., Šindlerová, L., Machala, M., Kozubík, A.:

Využití inkorporace 5´-bromdeoxyuridinu pro stanovení účinků polycyklických aromatických uhlovodíků na buněčný cyklus a proliferaci

Analytická cytometrie II., Brno, 11. – 14. 5. 2003

In: Sborník abstrakt, p. 108-109

Vondráček, J., Plíšková, M., Vojtěšek, B., Kozubík, A., Machala, M.:

Polycyclic aromatic hydrocarbons stimulate cell proliferation of human breast cancer MCF-4 cells

FEBS Special Meeting 2003 on Signal Transduction, Brussels, Belgium, 3. – 8. 7. 2003

In: Eur. J. Biochem., 270 (Suppl. 1), 2003, 127-128

Vondráček, J., Plíšková, M., Vojtěšek, B., Kozubík, A., Machala, M.:

Proliferation of human breast carcinoma MCF-7 cells induced by polycyclic aromatic hydrocarbons – The role of estrogen receptor-alpha and p53 protein

XXII. Xenobiochemické sympózium, Smolenice, Slovak Republic, 9. – 11. 6. 2003

In: Zborník príspevkov, p. 36-37

Vorlíčková, M.:

Abeceda struktur DNA

Symposium teoretické a aplikované biofyziky, České Budějovice, 18. – 20. 9. 2003

In: Program a souhrny sdělení, p. 57

Výkruta, M., Kypr, J.:

A novel method to characterize similarity of base stacking in DNA

Študentská vedecká konferencia, Bratislava, Slovak Republic, 9. – 10. 4. 2003

In: Zborník abstraktov prác diplomantov a doktorandov, p. 97

Vyskot, B.:

Plant sex chromosomes: a cytogenetic point of view

University of Alaska Fairbanks, Fairbanks, Alaska (U.S.A.), 6. 5. 2003

Vyskot, B.:

Modely vývojové biologie rostlin

3. metodické dny, Žďárské vrchy – Milovy, 20. – 24. 10. 2003

In: Biologické listy, 68, 2003, 253-261

Vyskot, B.:

Epigenetická dědičnost

Pokroky v molekulární biologii (kurz), Ústav molekulární genetiky AV ČR, Praha, 3. – 14. 11. 2003

Vyskot, B.:

Srovnávací vývojová biologie

Pokroky v molekulární biologii (kurz), Ústav molekulární genetiky AV ČR, Praha, 3. – 14. 11. 2003

Vyskot, B.:

Epigenetic mechanisms of cellular memory

XVIIth Biological Days. Memory in Living Systems, Brno, 19. – 20. 11. 2003

In: XVIIth Biological Days. Memory in Living Systems, p. 37-38

Vyskot, B., Lengerová, M., Hobza, R.:

Plant sex chromosomes: A cytogenetic's point of view

Plant Reproduction: From Mendel to Molecular Biology, Brno, 1. – 3. 9. 2003

In: Book of Abstracts, p. 28

Weiterová, L., Hofer, M., Pospíšil, M.:

Myelosuprese vyvolaná kombinovaným působením ionizujícího záření a karboplatiny. Ochranné působení látek zvyšujících extracelulární adenosin a G-CSF

Symposium teoretické a aplikované biofyziky, České Budějovice, 18. – 20. 9. 2003

In: Program a souhrny sdělení, p. 58

Zelníčková, P., Kovářů, F., Kovářů, H., Lojek, A., Svoboda, M.:

Postnatal development of oxidative burst and some surface markers of blood phagocytes

1st European Workshop on the Analysis of Phagocyte Functions, Brno, 7. – 9. 9. 2003

In: Final Program & Book of Abstracts, nestr.

Zemánek, M., Fialová, M., Vorlíčková, M.:
Konformační vlastnosti trinukleotidových motivů (TTG)n a (CCA)n: Formování, stabilita a kompetice tetraplexů a klasického heteroduplexu
Symposium teoretické a aplikované biofyziky, České Budějovice, 18. – 20. 9. 2003
In: Program a souhrny sdělení, p. 59

Zemánek, M., Fialová, M., Vorlíčková, M.:
Conformational properties of DNA containing (CCA)n/(TGG)n trinucleotide repeats
Študentská vedecká konferencia, Bratislava, Slovak Republic, 9. – 10. 4. 2003
In: Zborník abstraktov prác diplomantov a doktorandov, p. 99

Žlůvová, J., Nicolas, M., Negrutiu, I., Moneger, F.:
Which genes are responsible for dioecy in Silene?
Plant Reproduction: From Mendel to Molecular Biology, Brno, 1. – 3. 9. 2003
In: Book of Abstracts, p. 17

Žlůvová, J., Široký, J., Shippen, D. E., Vyskot, B., Říha, K.:
Genome instability and rDNA rearrangements in telomerase deficient Arabidopsis
Cold Spring Harbor Meeting on Telomeres & Telomerase New York, New York (U.S.A.), 30. 4. – 4. 5. 2003
In: Abstracts of papers, p. 162

D. OVERVIEW OF PUBLICATION ACTIVITIES IN 2003

1. Full-length papers	72
- supplementary, due to 2002	1
2. Short communications	2
3. Popularizing articles	4
4. Lectures - presented in the CR	4
- presented abroad	16
5. Lectures presented at conferences:	
National	72
International in the CR	49
International abroad	88
6. Abstracts of conferences:	
National	72
International in CR	49
International abroad	88
7. Lectures published in full extenso	9
8. Patent adicted abroad	1

IV. INTERNATIONAL CONTACTS

As always, international contacts were established in connection with research projects, supported by various grant agencies both from the Czech Republic and from abroad, on the basis of competitions organized by the Academy of Sciences of the Czech Republic (hereafter the Academy of Sciences CR or AS CR) or at the invitation of foreign institutions, etc.

An overview of international contacts in 2003 is provided in tables as follows:

Travels of scientists abroad

Country	*AS CR competition*	*Grants*	*Other sources*
Australia		3	
Belgium	1	2	1
Brasilia	1	1	
Bulgaria	1		1
Canada			2
Finland	3		
France		2	6
Germany		6	4
Great Britain		8	7
Greece		4	
Israel	1	1	
Italy		14	3
Korea	1		
Luxemburg		2	
Mexico		2	
Poland		3	1
Russia		1	
Slovak Republic	5	19	9
Spain	2	6	
Switzerland		1	2
The Netherlands		4	
Turkey			1
USA		7	9
Total	15	86	46

Foreign guests

Country	*AS CR competition*	*Grants*	*Other*	*Conferences*
Austria			1	
Bulgaria		1	1	
Finland		1		
France		3		
Germany		1		10
Great Britain		2		
Greece			1	
Hungary		1		1
Israel		1		
Italy		2		1
Poland		1		
Russia		1		
Slovak Republic		10		13
Spain		2	2	
Switzerland		1		
The Netherlands			1	
Turkey		3		
Ukraine		1		
USA		1		1
Total		32	6	26

A. Overview of international co-operations of the Institute of Biophysics and foreign grants in 2003

Joint research based on direct agreements with foreign laboratories and projects which received grants from abroad continued as shown below.

1. Direct agreements with foreign laboratories

BULGARIA
Institute of Oceanology, BAS, Varna
A. Lojek - Oxidant/antioxidant properties of marine biota - indication for coastal marine environment and human health assessment

FINLAND
University of Turku, Department of Biochemistry, Turku
A. Lojek - Role of phagocytes in the oxidative injury of animal cells and tissues

GERMANY
november AG, Erlangen
E. Paleček - Collaborative research and development agreement on electrochemical DNA-sensors

GREAT BRITAIN
Queen Mary and Westfield College, University of London
A. Kovařík - Research in the field of plant genetics and epigenetics

SLOVAK REPUBLIC
Institute of experimental physics, Slovak Academy of Sciences, Košice
A. Kozubík – Investigation of biological membranes a their models, structure and stability of nucleic acids and proteins, their interaction with drugs
Institute of Biological and Ecological Sciences, Faculty of Natural Sciences, P. J. Šafárik University, Košice
A. Kozubík – Regulation, proliferation, differenciation and apoptosos in tumor cell populations *in vitro* and *in vivo*

USA
Virginia Commonwealth University, Richmond
V. Brabec - Mechanistic studies on new platinum clinical agents

2. Foreign Grants

ARGENTINA
Grupo de Innovación Tecnologica en la Universidad de Buonos Aires
L. Novotný (IFCH JH AV CR Prague), E. Paleček (2002 - 2004) – Interaction of peptides, proteins and DNA with electrodes and new electrochemical methods for biochemistry and molecular genetics

FRANCE
KONTAKT Program, MEdYS CR, STC CR/Greece, ES 022
Université René Descartes, UMR, CNRS, Paris
V. Brabec (2002 – 2003) – DNA interstrand cross-links of platinum: antitumour activity of cisplatin?
CNRS/AS CR Collaboration, Institute Jacques Monod, Paris
M. Štros (2003 - 2004) – Alternative structures of the DNA and the function of eukaryotic genomes

GERMANY
Bundesministerium für Wirtschaft und Technologie,SIRS Laboratorium, Jena
M. Čížˇ, A. Lojek (2003 – 2004) – Immuno-Arraytor: Biochip-based *in vitro*-diagnostics as a modern tool for the early identification of primary complications after organ transplantations

GREAT BRITAIN
The Wellcome Trust, 062366/Z/00/Z
V. Brabec (2000 - 2003) - DNA interactions of platinum anticancer drugs. Relation to the development of new cytostatics
The Leverhulme trust F/07476/G
J. Fajkus (2001 - 2004) - Loss and gain of typical telomere repeats in a major radiation of monocots
Senior Wellcome Trust International Research Fellowship for Biomedical Research in Central Europe, GR067507MF
J. Šponer (2003 - 2007)

GREECE
KONTAKT Program, MEdYS CR, STC CR/Greece, ME 685
Laboratory of Physical Chemistry, Department of Chemistry, Aristotle University, Thessalonica
V. Vetterl (2003 - 2005) Develoment of methods and construction of sensors for the detection of DNA-drug interactions
KONTAKT Program, MEdYS CR, STC CR/Greece, RC-3-24
Laboratory of Physical Chemistry, Department of Chemistry, Aristotle University, Thessalonica

ITALY
KONTAKT Program, MEdYS CR, STC CR/Italy, No. 16
Universita Cattolica del Sacro Cuore, Roma
M. Číž (2002 - 2004) - Chemiluminescent determination of the role of neutrophils in the development of oxidative stress-induced injury

JAPAN
KONTAKT Program, MEdYS CR, STC CR/Japan, ME 565
Department of Life Science, Faculty of Bioresources, Mie University, Mie
S. Kozubek (2002 - 2006) - Structure and function of interphase chromosomes in normal and malignant cells

RUSSIA
Committee for collaboration with Joint Institute for Nuclear Research, Dubna
S. Kozubek (1999 - 2003) – The structure of cell nuclei and its relation to genetic changes induced by densely ionising radiation in cells
Committee for collaboration with Joint Institute for Nuclear Research, Dubna
S. Kozubek (2002 - 2004) - Estimation of the risk of chronic myeloid leukemia from low levels of radiation

SLOVAK REPUBLIC
KONTAKT Program, MEdYS CR, STC CR/SR, 198
Institute of experimental pharmacology, SAS, Bratislava
A. Lojek (2002 - 2003) - Antioxidative properties of cationic amphiphylic drugs and endogenous mediators of blood platelets

USA
Howard Hughes Medical Institute (HHMI), INTNL 55000313
J. Kašpárková (2001 - 2005) - Basis for new structure - pharmacological relationship of platinum antitumor drugs

Other fundings

COST OC D20.001
V. Brabec (2001 - 2005) - Biochemistry, structural and cell biology of anticancer platinum drugs of second generation
COST OC D21.001
V. Brabec (2002 - 2005) - Characterisation of metalloproteins, key molecules in biological processes
COST OC D20.003
V. Brabec (2002 - 2005) - Intracellular and extracellular target sites for anti-cancer activity and toxiciry of ruthenium complexes

COST OC D21.002
E. Paleček (2002 - 2005) - Characterisation of metalloproteins important in cancer and their interaction with DNA
COST OC D20/010/02
O. Nováková (2003 – 2005) – Strategy of non-covalent recognition of DNA for design and synthesis of new metal-based drugs

FP5 Research Training Network Project of EU
Co-ordinator: Michael Hannon, UK; Participant: *V. Brabec* (2003 - 2006) - Structural effects arising from major groove DNA recognition by metallo-supramolecular cylinders

UNESCO
J. Jursa (2002 - 2003) - Biological databases for academic community served by the national Node of the ICCBnet (International Center for Cooperation in Bioinformatics network), Czech Republic

B. Co-Operations with international governmental and non-governmental organizations

J. Šlotová is a representative of the CR in the ICSU
S. Kozubek is a chairman of the Czech Committee for Biophysics, *V. Brabec, E. Paleček, J. Šlotová* and *V. Vetterl* are members of this Committee
V. Brabec is a representative of the CR in the Managing Board of the European Program of Scientific and Technological Research, COST D20 and D21, and a member of the Evaluation Commission of the 5th EC Framework Program in Brussels, Belgium
J. Fajkus is an expert for evaluation of the projects of 5FWP EC „Quality of Life“ in Brussels, Belgium
S. Kozubek is a member of the Programs Advisory Committee, Joint Institute for Nuclear Research, Dubna, Russia and is an expert for evaluation of the projects of 5FWP EC „Genetics and disseases of genetic origin“ in Brussels, Belgium

C. International conferences organized by Institute of Biophysics

2nd Workshop on Biophysics of the Genome, Hlohovec at Břeclav, 2 - 4 April 2003

Analytical Cytometry II, Brno, 11- 14 May 2003
Co-organisers: Czech Society for Analytical Cytology in collaboration with MU, UOC and MOU, Brno

XIth International Congress of Plant Embryology: From Mendel to Molecular Biology, Brno, 1 - 3 September 2003
Co-organiser: Institute of Biophysics AS CR, Brno

1st European Workshop on the Analysis of Phagocyte Functions, Brno, 7 - 9 September 2003

Symposium on Theoretical and Applied Biophysics, České Budějovice, 18 - 20 September 2003
Co-organisers: IUPAB Czech Committee and University of South Bohemia, České Budějovice

Methods in Plant Sciences, Symposium 2003, Milovy, 20 - 23 October 2003
Organiser: Institute of Experimental Botany AS CR, Prague in collaboration with Institute of Biophysics AS CR, Brno

V. DOCTORAL STUDIES, CO-OPERATION WITH UNIVERSITIES AND OTHER ACTIVITIES

A. Postgraduate studies

In 2003, the Institute of Biophysics successfully continued to participate in postgraduate education (doctoral studies - DSP) at universities, mainly at the Faculty of Science of Masaryk University in Brno. In total, sixty six students worked towards a doctor's degree at the IBP. Seventeen of them were external or combined postgraduate students, forty two of them were internal students and 7 students interrupted their studies.

Total number of students	*External/ /combined*	*Internal*	*Year*
9	2	7	I.
12	1	11	II.
16	2	14	III.
8	5	3	IV.
1	1	0	V.
3	3	0	VI.
10	3	7	absolvents

DSP students belong to fields of specialization as follows:

biophysics (15); 1 student accomplished her Doctor's Theses students, 2 students their study interrupted
molecular biology (27); 3 students accomplished their Doctor's Theses and 4 students their study interrupted
genetics (8); 2 students accomplished their Doctor´s Theses
animal physiology (7); 2 students accomplished their Doctor's Theses students, 1 student his study interrupted
immunology (4)
environmental chemistry (2); 1 student accomplished her Doctor's Theses students
botany (1); 1 student accomplished his Doctor´s Theses
anatomy and physiology of plants (1)
microbiology (1)
medical biophysics (1)
18 scientists of the IBP were appointed as PGS student advisors

Doctoral Theses - undertaken at the IBP and defended in 2003:

J. Amrichová: Topography of telomeres in the nuclei of human lymphocytes and its realtionship to the structure of chromosomal territories

A. Gaňová: Functional aspects of spatial structure of the human genome

J. Guo: Tightly regulated extression of *isopentenyl transferase* (*ipt*) gene in transgenic *Arabidopsis thaliana*: System development and impact of *ipt* transcription activation on Arabidopsis development

K. Chramostová: Mechanisms of non-genotoxic carcinogenesis and their investigation slected cellular models *in vitro*

M. Lengerová: Structure and evolution of the sex chromosomes in dioecious plants *Silene latifolia* and *Rumex acetosa*

M. V. Marini: Biophysical analysis of DNA modified by platinum complexes in relation to their chemotherapeutical properties

M. Skleničková: Biology of telomeres in oncological diagnostics

K. Souček: Regulation of apoptosis induced by *all-trans* retinoic acid in cells of acute promyelocyte leukemia

R. Taslerová: Genome architecture in cells of Ewing sarcoma and chronic myeloid leukemia

A. Vaculová: Role of fatty acids and endogenous regulators of apoptosis in modulation of the death of colon cancer cells

The following scientists of the IBP are members of Branch Councils (BC) for postgradual studies at the Faculty of Science of Masaryk University in Brno:

BC for PGS Physics: *V. Brabec* (garant for PGS biophysics)
BC for Biophysics: *V. Brabec* (chairman), *S. Kozubek, J. Šlotová, V. Vetterl (members)*
BC for Biology: *B. Vyskot*
BC for Molecular and Cell Biology: *J. Fajkus, J. Kypr, E. Paleček, V. Vetterl*
BC for Physiology and Developmental Biology of Animals: *J. Hofmanová, A. Kozubík*
BC for Immunology: *M. Číž, A. Lojek*
BC for Genetics: *B. Vyskot*
BC for Environmental Chemistry and Ecotoxicology: *J. Hofmanová, A. Kozubík*
BC for Biochemistry: *J. Šponer*

In addition to this, IBP scientists are members of these of Branch Councils at other faculties:

Faculty of Medicine, Masaryk University in Brno:
BC for Biophysics: *V. Vetterl*
BC for Molecular Biology: *V. Vetterl*

Faculty of Medicine, Palacký University in Olomouc:
BC for Medical Biophysics: *V. Vetterl*

Faculty of Science, Palacký University in Olomouc:
BC for Physical and Analytical Chemistry: *E. Paleček, V. Vetterl, O. Vrána*
BC for Botany: *B. Vyskot*

Faculty of Science, Charles University in Prague:
BC for Anatomy and Physiology of Plants: *B. Vyskot*

Faculty of Mathematics and Physics, Charles University in Prague:
BC for Molecular and Biological Structures: *V. Brabec*

B. Co-operation with Universities

Masaryk University in Brno:
S. Kozubek is a member of the Scientific Council
Faculty of Science, Masaryk University in Brno:
J. Šlotová is a member of the Scientific Council
Faculty of Medicine, Masaryk University in Brno:
J. Šlotová is a member of the Scientific Council

Palacký University in Olomouc:
B. Vyskot is a member of the Scientific Council

Faculty of Science, Palacký University in Olomouc:
V. Brabec is a member of the Scientific Council

P.J. Šafárik University, Košice, Slovak Republic
Faculty of Science:
A. Kozubík is a member of the Scientific Council

In 2003 there was completed habilitation of *J. Fajkus*, *S. Kozubek* (at Faculty of Science, Masaryk University in Brno) and of *O. Vrána* (Faculty of Science, Palacký University in Olomouc), all of them were nominated as assistant profesors.

C. Membership in scientific institutions

M. Bezděk is a member of the Czech Committee for Transgenic Plants
M. Hofer is a member of the Branch Committee 3 "Medical Sciences" and a member of the Sub-branch Committee 305 "Physiology, pharmacology, toxicology" of the Grant Agency CR and is a member of the Branch Council for

Theoretical Medical Fields and Pharmacy at the J. E. Purkyně Military Medical Academy in Hradec Králové

J. Hofmanová is a member of the Branch Council 6 "Ecological and Biological Sciences" of the Grant Agency AS CR

F. Jelen is a member of the Branch Council 4 "Chemical Sciences" of the Grant Agency AS CR

J. Jursa is a member of the South Moravian Regional Committee for Computer Technology and a member of the Council for Computer Technology of the AS CR

S. Kozubek was elected a member of the General Assembly of the AS CR for the period 2003 – 2005, a member of the Director Advisory Board of the State Office for Nuclear Safety and is a Co-ordinator of the Consorcium for DNA microarrays

A. Kozubík is a member of the Scientific Council of the Masaryk Oncological Institute, Brno, a member of the Co-ordination Committee of the University Oncological Centre, Brno and a member of the Scientific Council of the program RECETOX at the Faculty of Science, MU Brno

J. Kypr is a member of the Sub-branch Committee 301 "Molecular Biology, Genetics and Experimental Oncology" of the Grant Agency CR

A. Lojek is a member of the Branch Committee 5 " Agricultural Sciences" and the chairman of the Sub-branch Committee 524 "Physiology and Pathology of Animals" of the Grant Agency CR

E. Lukášová is a member of the Sub-branch Committee 202 "Physics" of the Grant Agency CR

E. Paleček is a member of the Scientific Council of the AS CR, is a member of the Branch Council 5 "Molecular and Cell Biology" of the Grant Agency AS CR, a member of the Supervisory Committee of the GA AS CR, a founding member of the Learned Society of the Czech Republic, a member of the Bioethical Committee at the Council of the Government of the CR for research and development, a member of the permanent working group (for biology and ecology) of the Accreditation Committee of the Government of CR for the Universities and a member of the Ministry of Education, Youth and Sport CR Committee for evaluating research plans and results of institutions for granting institutional support to research and development in science

J. Šlotová is a vice-chairman of the Council for International Affairs of the AS CR and a member of the General Assembly of the AS CR

V. Vetterl is a member of the Branch Council 4 "Chemical Sciences" of the Grant Agency AS CR

M. Vojtíšková is a member of the Council for qualification degrees in Genetics of the Ministry of health of the CR

M. Vorlíčková is a member of the Branch Council 1 "Mathematical and Physical Sciences, Informatics" of the Grant Agency AS CR

O. Vrána is a vice-chairman of the Branch Council 5 "Molecular and Cellular Biology " of the Grant Agency AS CR

B. Vyskot is a member of the Accreditation Committee of the Government of the CR for the Universities and chairman of its working group for biology and

ecology, a member of the Learned Society of the Czech Republic and a member of board for doctor's degree (DSc.) in molecular biology, genetics and biology of plants

V. Brabec is a member of the Slovak board for doctor's degrees in molecular biology

The following scientists were members of editorial boards of scientific journals:

V. Brabec - Bioorganic Chemistry and Applications
E. Paleček - General Physiology and Biophysics, Bioelectrochemistry and Bioenergetics and Talanta (Guest-editor)
J. Šponer - Journal of Biomolecular Structure and Dynamics (Senior Editor)
V. Vetterl - Czech Journal for Physics

D. Membership in scientific societies

International scientific organizations and societies:

V. Brabec - member of the Biophysical Society USA, of the Society of Biological Inorganic Chemistry and of the American Society for Biochemistry and Molecular Biology
V. Brázda - member of The Biochemical Society
B. Brzobohatý - member of the Federation of European Societies of Plant Physiology, of the Society for Experimental Biology, of the International Plant Growth Substances Association and of the American Society of Plant Biologists
M. Číž - member of the Society for Free Radical Research
H. Čížová - member of The Oxygen Society
J. Fajkus - member of the American Association for Microbiology
J. Fulneček - member of the DNA Methylation Society
E. Frimlová - member of the Federation of European Societies of Plant Physiology
J. Hejátko - member of the American Society of Plant Biologists
M. Hofer - member of the Council of European Society for Radiation Biology
J. Hofmanová - member of the European Tissue Culture Society, of the International Society for Analytical Cytology and of the International Society for Predictive Oncology
J. Kašpárková – member of the Society of Biological Inorganic Chemistry and of the American Association for the Advancement of Science
S. Kozubek - member of the European Society for Radiation Biology
A. Kozubík - member of the European Tissue Culture Society, of the Society for Leukocyte Biology (USA), of the International Society for Analytical Cytology and of the International Society for Predictive Oncology
A. Lojek - member of the Society for Free Radical Research
E. Paleček - member of the Bioelectrochemical Society and of the New York Academy of Sciences

M. Pospíšil - member of the International Astronautical Academy and of the European Society for Radiation Biology
M. Štros - member of the American Society for Biochemistry and Molecular Biology
V. Vetterl - member of the Bioelectrochemical Society and of the International Society of Electrochemistry
M. Vorlíčková - member of the Biophysical Society USA
A. Vacek - member of the International Astronautical Academy
J. Zouhar - member of the American Society of Plant Biologists

National scientific organizations and committees:

M. Bezděk - member of the of the Czech Society for Biochemistry and Molecular Biology and of the Mendel Genetic Society
V. Brabec - member of the Czech Committee for Biophysics (IUPAB)
B. Brzobohatý - member of the Czech Society for Biochemistry and Molecular Biology and of the Society for Experimental Plant Biology
M. Číž - member of the Czech Society for Biochemistry and Molecular Biology
H. Čížová - member of the Czech Society for Biochemistry and Molecular Biology
J. Fajkus – board member of the Mendel Genetic Society
M. Fojtová - member of the Society of Experimental Plant Biology
E. Frimlová - member of the Society of Experimental Plant Biology
M. Hofer - board member of the Czech Radiobiological Society at the Czech JEP Medical Society
J. Hofmanová - member of the of the Society for Tissue Cultivation at the Czech Oncological Society, of the Czech Radiobiological Society at the Czech JEP Medical Society and founding member of the Czech Society for Analytical Cytometry
B. Koukalová - member of the Mendel Genetic Society and of the Czech Biological Society
A. Kovařík - member of the Society of Experimental Plant Biology and of the Mendel Genetic Society
S. Kozubek - chairman of the Czech Committee for Biophysics (IUPAB), board member of the Czech Radiobiological Society at the Czech JEP Medical Society, member of the National Committee for the Exploitation and Research of Cosmic Space and a member of the Advisory Board of the State Office for Nuclear Safety
A. Kozubík - member of the Society for Tissue Cultivation at the Czech Oncological society, of the Czech Radiobiological Society at the Czech JEP Medical Society and founding member of the Czech Society for Analytical Cytometry
L. Kubala - member of the Czech Society for Biochemistry and Molecular Biology
A. Lojek - member of the Czech Immunological Society
E. Paleček - member of the Czech Committee for Biophysics (IUPAB)
J. Šlotová - member of the Czech Committee for Biophysics (IUPAB)
M. Štros - member of the Czech Society for Biochemistry and Molecular Biology

V. Vetterl - board member of the of the Chemical Physics and Biophysics Branch of the Union of Czech and Slovak Mathematicians and Physicists and member of the Czech Committee for Biophysics (IUPAB)

M. Vorlíčková - member of the Czech Society for Biochemistry and Molecular Biology

O. Vrána - chairman of the Biophysical Section of the Czech Biological Society

J. Vondráček - member of the Czech Immunological Society and of the Czech Society for Biochemistry and Molecular Biology

B. Vyskot – board member of the Plant Biotechnology Section of the Czech Biotechnological Society