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BioCeV

EUROPEAN UNION
EUROPEAN REGIONAL DEVELOPMENT FUND
INVESTING IN YOUR FUTURE

2007–13
OP Research and Development for Innovation

Biotechnology and Biomedicine Centre of the Academy of Sciences and Charles University in Vestec

CENTRAL BOHEMIA, CZECH REPUBLIC

BioCeV

Foreword

Biomedicine and biotechnologies today lie within intensely evolving fields that enable this generation to live more contentedly than ever since they affect the environment, medicine, health care standards and thus the quality of human life.

Knowledge resulting from these branches has now become a significant part of our everyday life, while the increasing demands of the population on longevity and quality of being focus interest worldwide on the importance of these branches as they unveil the potential for improved quality of living.

Both fields could not exist nor develop without high-end basic research which precedes practical applications, such as new environmental processes, diagnostic and treatment procedures or the development of new pharmaceuticals that treat numerous diseases considerably more effectively and safely.

It will then be possible to follow up with action leading to adaptation for commercial use since it is based on the results of basic research advanced by numerous residents at universities and research institutes which are developing basic patterns and mechanisms of living organisms at the level of genes and singular molecules and cells up to whole of organisms.

Markets value highly the interconnection of front-end basic research requiring the most qualitative and the most talented scientists and cutting edge technologies. With their ability to transfer knowledge into innovation and practical applications, they will provide us the opportunity to reach the high impact effects offered by today's knowledge of biomedicine and biotechnologies.

The solution to this opportunity is BIOCEV – the Biotechnology and Biomedicine Centre of the Czech Academy of Sciences and Charles University in Vestec.

The BIOCEV project, originating in the Czech Republic with support from the European Union, is a joint project of this country's two most prestigious research and educational institutions, recently acknowledged as such by SIR World Report 2010. The project's aim is to create a unique place for cooperation of top scientists in basic research and biotechnology and biomedicine teams as well as business professionals who will be working jointly on such practical and innovative outputs as new pharmaceuticals for veterinary and human medicine. There will be a strong emphasis in BIOCEV on the quality of basic research and its transfer into practise. But with both excellent research and an effective knowledge transfer, BIOCEV, due to its unique infrastructure and tailor-made educative programmes, will be able to offer more. This will include an excellent educational establishment generating new professionals well-educated in the latest biotechnology and biomedicine methods. These will represent a necessary premise for the development not only of research but also of biotechnology and biomedicine industries in the Czech Republic and abroad.

This brochure will guide you through our research programmes and projects as well as the services of our distinctive infrastructure, also scheduled to be at your service in BIOCEV. We believe our research programmes will provide you a clearer perspective into what we do and we hope will inspire you to cooperate with us in the future.

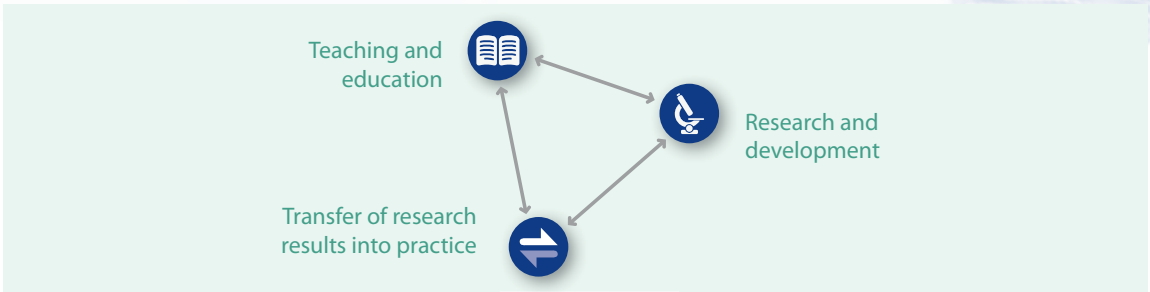
Jan Rajnoch, Project Director

Project vision

To establish a centre of excellence as part of the European Research Area and to guarantee development of modern biotechnologies and biomedicine in favour of scientific progress and modern society.

Main pillars of the project

The project BIOCEV builds upon three pillars of the knowledge triangle.



The **research programme**, which provides scientific outputs of highest quality, stands above all. It stems from the intellectual potential and originality of the strictly selected research teams as well as the establishment of the state-of-the-art core facilities. The research projects involve five fundamental areas: Functional Genomics, Cellular Biology and Virology, Structural Biology and Protein Engineering, Biomaterials and Tissue Engineering and Development of Diagnostic and Therapeutic Procedures.

Transfer of research results into practice represents the second pillar of BIOCEV. The centre will focus on intensive collaboration with the commercial sphere and will support preservation of intellectual property and its further utilization. The forms of collaboration with commercial partners will namely include: commercialization of intellectual property, exploitation of expert support of the core facilities, in-house contractual research conducted by BIOCEV research laboratories, establishment of common training/demonstration facilities and study exchange of researchers.

The results of scientific research of BIOCEV will be the basis particularly for new diagnostic procedures and development of new therapeutic modalities. Generation of the new knowledge basis together with the unique BIOCEV infrastructure will provide biotech companies with an exceptional way of cooperation in the form of contractual research and with professional staff training in the advanced biotechnology methods.

The third pillar is **teaching and education** namely of PhD students, which will be achieved within current study programmes of Charles University and by newly accredited programmes in biotechnology and biomedicine. In addition, BIOCEV will organize and facilitate specialized international courses for Czech and international students and young scientists. The new centre will also offer training for business employees in advanced biotechnology methods.

1. FUNCTIONAL GENOMICS

Programme Leader: Radislav Sedláček
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Research Laboratories: 7

Programme description

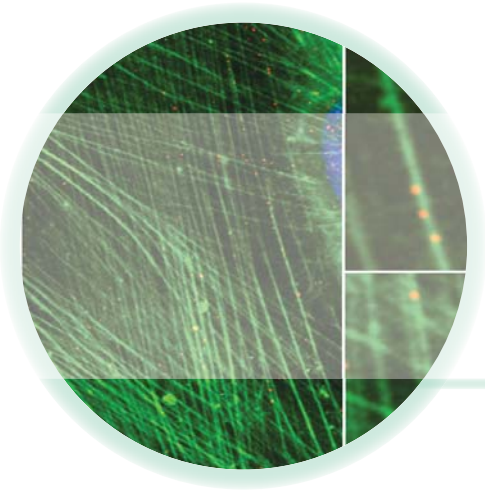
One of the key challenges in biomedical research is to attribute biological functions to all identified human genes. In the postgenomic era, in which genes and genomic organization of the human and other genomes were identified, there is a huge demand to assign the function of individual genes in their complex networks. Laboratory mouse and rat have become essential experimental models for this functional annotation of human genome. The programme *Functional Genomics* will be built on pillars for which an all-encompassing term of *'phenogenomics'* can be used. These pillars involve functional and comparative genomics combined with genetic engineering. The thematic part of the programme will focus on areas of metabolic diseases accompanied with studies in liver, cardiovascular systems, and on analysis of auditory (hearing) and visual (eye) organs. The programme will be supported by the central platform for phenotyping, transgenesis, and archiving (CCP) that enables the researches to develop dual activity: to identify genes vital for the function of specialized physiological systems and to validate them as therapeutic targets.

Application potential

Supported from a robust and standardized phenotyping platform offering a functional screening of almost all physiologic body systems, the groups of this programme aim to identify and characterize genes representing new potential targets to treat various human diseases. Main effort focuses on metabolic syndrome and physiologic functions interrelated with this complex human disease. Identified genes and genetic determinants will be then scrutinized for their potential to employ them as therapeutic targets. Beside the liver and metabolic disorders, research projects will focus also on visual and auditory systems whose correct functions is of enormous importance for human's life quality and well-being. Genes important for the physiologic systems will be identified, examined, and prove whether they could serve as a diagnostic markers or therapeutic targets. Once the therapeutic potential is proved researches will together with drug developing groups or companies study the drug efficacy employing the know-how, capacity, and experimental models of the CCP.

Research outcomes

- Establishment of an expert centre for phenogenomics, the Czech Centre for Phenogenomics (CCP), that builds on three pillars: generation of mutant models, their phenotype analysis, and their archiving and distribution
- Building a national node for functional annotation of genes within the frame of European infrastructures INFRAFRONTIER and EMMA; this platform will provide services for analyses of phenotypes of mutant models using bottom-up and top-down principles
- Description of genetic determinants of cardiovascular and metabolic failures that often occur simultaneously and are diagnosed as a metabolic syndrome
- Identification of genes, which are involved in the function and disease of the liver and influence the development of the metabolic syndrome; generation of conditional mouse mutants to reveal their specific liver functions
- Elucidation of the genetic background of inherited or age-related hearing loss employing mouse genome analysis and generation of mouse mutant models
- Generation of transgenic Cre-recombinase mice to study functional genomics of the early retina and adult cornea
- Characterization of the Wnt signalling pathway in the eye tissues
- Revealing the function of individual lipocalins



2. CELLULAR BIOLOGY AND VIROLOGY

Programme Leader: Jan Tachezy
tachezy@natur.cuni.cz

Research Laboratories: 22

Programme description

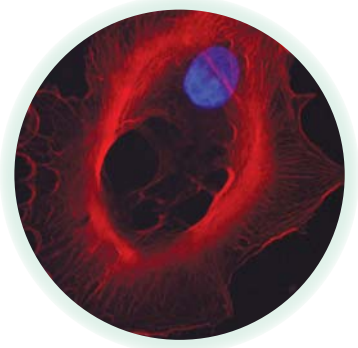
This programme includes four synergic and mutually complementing sub-programmes: Eukaryotic Microbiology, Biology of Cancer Cells, Virology and Structure and Differentiation of Mammalian Cells. These sub-programmes cover a large spectrum of eukaryotic cells ranging from the unicellular pathogens (parasitic protists) and unicellular eukaryotes forming multi-cellular assemblies (yeasts) to mammalian cells and tissues, as well as interactions between eukaryotic cellular structures and simple intracellular parasites - viruses. The project involves establishment of laboratories for studying eukaryotic pathogens, viruses and tumour cells using top imaging technology of the future centre of European infrastructure Euro-BioImaging. In addition to scientific goals, the accreditation of new doctoral programmes in the fields of Eukaryotic Microbiology and Biomedicine will be prepared.

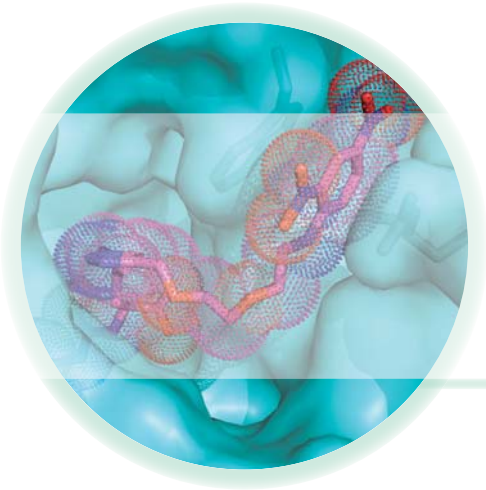
Application potential

The cellular biology research represents a leading discipline of modern science and as such it has a great potential for innovation in biomedicine and biotechnology. The programme will comprise study of the association of tumour diseases with viral infections, molecular mechanisms of microorganism interactions and pathogen-host signalling, potential of gene therapy and vaccination namely against viral infections. Expected application outputs include antiparasitic, antimycotic and antitumour agents, antiviral vaccines, novel treatment approaches and biomodulators.

Research outcomes

- Identification of unique cellular functions related to the pathogenesis and parasitic way of life of selected parasitic protists and comparison with their free-living relatives
- Identification of unique cellular functions related to the multicellular development in the pathogenic and nonpathogenic yeasts, their interaction with the host and functional characterization of the specific metabolites and signalling molecules
- Discovery of new molecules that will be applicable as cell biology tools with a possible pharmacological potential
- Understanding the mechanisms of invasiveness of cancer cells and characterization of membrane proteases in relation to oncogenesis
- Understanding the interactions between viruses and cellular structures during viral infections, mechanisms of stress and defence responses, mechanisms of deregulation of cellular processes including malignant transformation
- Development of effective carriers for the introduction of heterologous DNA into target cells
- Development of preventive antiviral and anticancer vaccines
- Identification of the structural elements of the cell nucleus and function of these elements during the regulation of gene expression
- Understanding o the mitochondrial structure in relation to its specific gene expression
- Characterization of selected receptors across eukaryotic organisms





3. STRUCTURAL BIOLOGY AND PROTEIN ENGINEERING

Programme Leader: Bohdan Schneider
bohdan.schneider@img.cas.cz

Research Laboratories: 10

Programme description

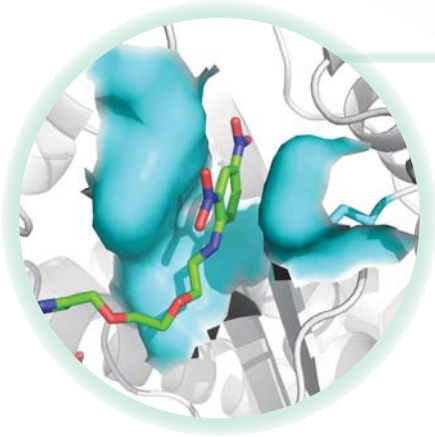
This programme is focused on research of novel biotechnologically, diagnostically, and medically important biomolecules, proteins and nucleic acids that will be constructed using state-of-the-art methods of molecular biology and protein engineering. Structures and activities of the studied molecules will be analyzed by complex biophysical methods, advanced spectrometry, and crystallography. Understanding structures of the studied molecules and their mutual interactions will help us to modify them so that their desired biological activities shall improve and it will be possible to use them for diagnostics of diseases, as drugs or as advanced materials.

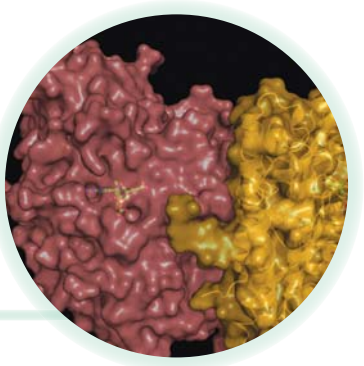
Application potential

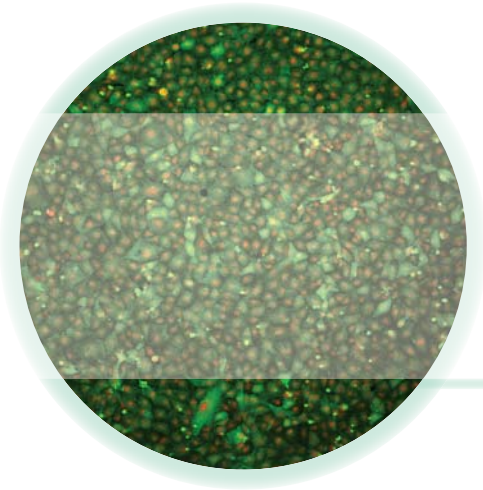
The programme opens wide possibilities for commercial outputs. For instance, newly developed recombinant proteins with high binding affinity to other molecules can function as novel antiviral or anticancer drugs or they can diagnose these diseases. Natural compounds will be modified with the goal to improve their antibiotic activity. Structural studies of enzymes will help increase efficiency of treatment of toxic wastes, support development of materials for green energy (biological cells), or of biotechnological treatment of food. A part of the programme focused on the development of fast, robust, and sensitive methods for mass spectrometric characterization of structural and topological properties of proteins will enable fast characterization and validation of generic biologics, biosimilars.

Research outcomes

- Modifications of the studied enzymes leading to their improved function, e.g. increased temperature stability or enzymatic efficiency
- Newly determined 3D structures
- Description of structure-activity relationships of molecules in the studied signalling pathways
- Development of procedures for improvement of ligand properties, design of new ligands
- Expertise in the research of biologics
- Explanation of the (non-)specificity of protein/DNA interactions at atomic and submolecular scale
- Proposed modifications of DNA and/or protein specifically influencing (increasing or decreasing) specificity of their interaction
- Development of novel mass spectrometry methods, application of these methods to determination of structural and topological properties of biomolecular systems
- Design and preparation of novel proteins developed to specifically bind to biotechnologically, diagnostically, and/or medically important molecules
- A physical model correctly predicting structures of thermodynamically stable proteins after their folding
- Bioinformatic tools for search of transposomal noncoding sequences (TN) and their regulatory elements
- Database describing various biologically and medically important aspects of TN







4. BIOMATERIALS AND TISSUE ENGINEERING

Programme Leader: Eduard Brynda
brynda@imc.cas.cz

Research Laboratories: 6

Programme description

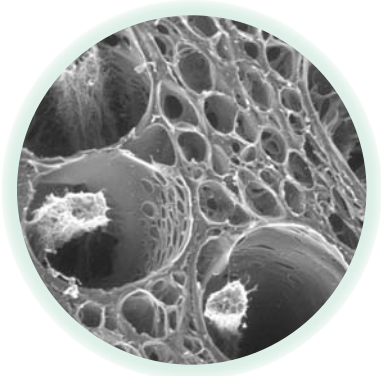
The programme is focused on advanced trends in medicine aimed at usage of sophisticated tissue prostheses systems composed of synthetic materials combined with specific biologically active compounds and cells for regeneration and replacement of diseased tissues and organs or for controlled drug and gene delivery targeted to specific tissues and cells in diseased organism. The programme feasibility is guaranteed by the close collaboration of "synthesis" teams concerned with the development and synthesis of artificial carriers for cells, therapeutics and diagnostics, and "biomedicine" teams concerned with applications of cells, including stem cells, development of bioartificial grafts for tissue engineering, and testing therapeutic and diagnostic systems. The basic common activities of the "synthesis" teams consisting in synthesis of polymer materials with attached biologically active components will be based in general on investigation and testing interactions of cells and tissues with the biomaterials directed to specific medical applications.

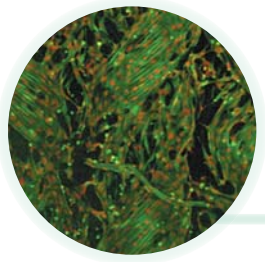
Application potential

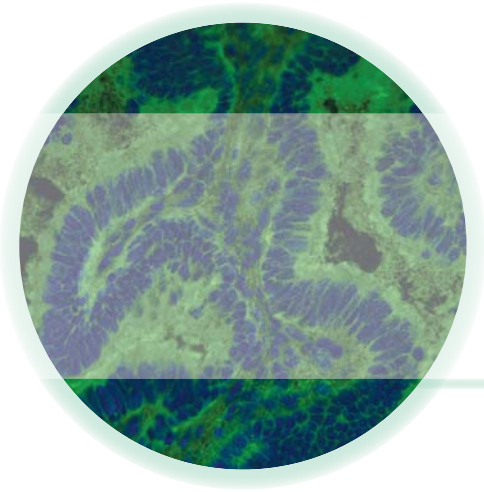
The overall aim of the applied research within this programme is to develop technologies for preparation of the intended products and to standardize this preparation so that it is possible to transfer these technologies over to clinical practice. Planned outputs include: bioartificial blood vessel, valve, bone, and cartilage grafts, scaffolds for therapy of spinal cord lesions, targeted drug, gene, and diagnostics delivery systems for therapy and diagnostics of cancer and cardiovascular diseases, biosensors and protein chips, and affinity carriers for separation and purification of biological fluids and suspensions.

Research outcomes

- New synthetic methods for controlled preparation of supramolecular dendritic, hyperbranched, star-shaped, and comb-like water-soluble polymer structures
- High-molecular water-soluble polymer transport systems for the targeted delivery of drugs, diagnostics, and their combinations
- In vitro and in vivo biological evaluation of new high-molecular-weight polymer conjugates in selected animal neoplastic and cardiovascular models
- Magnetic carriers based on polymethacrylates and polymethacrylamides, easily accessible for various chemical modifications enabling immobilization of biologically active molecules
- Anti-fouling polymer layers with covalently attached bioreceptors for SPR biosensors detecting selected analytes in the blood serum, plasma and blood
- Superporous biodegradable hydrogels as scaffolds for regeneration of soft tissues and replacements of cartilage and damaged spinal cord
- Newly constructed bioartificial tissue grafts (blood vessels, heart valve, bone, skin)
- Innovated grafts of blood vessel and bones prepared by modification of currently clinically used grafts
- Systems for targeted drug delivery
- Biosensors and stimulators of cell functions
- Protocols for stem cell differentiation into clinically relevant lines, clinical and preclinical studies to verify safety and efficacy, and tissue reconstruction methods
- Methods for separation, culture and differentiation of stem cells from human epidermis







5. DEVELOPMENT OF DIAGNOSTIC AND THERAPEUTIC PROCEDURES

Programme Leader: Pavel Martásek
pavel.martasek@gmail.com

Research Laboratories: 9

Programme description

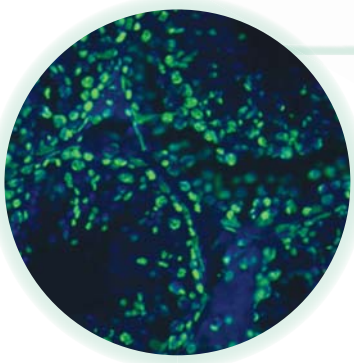
This programme includes a spectrum of projects covering reproductive medicine, diabetic complications, autoimmune and selected tumour diseases, inherited metabolic disorders, and study of heme pathology and of the effect of lack or excess of gaseous signalling molecules. The unifying element of all the projects is the study of the pathological condition of a cell, that is, finding out the causes of this condition, profiling the expression of the chosen genes, detecting changes in the localization and modification of the chosen proteins and identifying other molecules that relate to the induction of the pathology, furthering the development of new procedures for the prevention of the disease and creating new methods and diagnostics for monitoring the process of the disease and tools for the molecular therapy of the accompanying pathological condition.

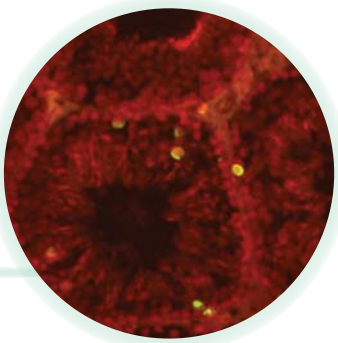
Application potential

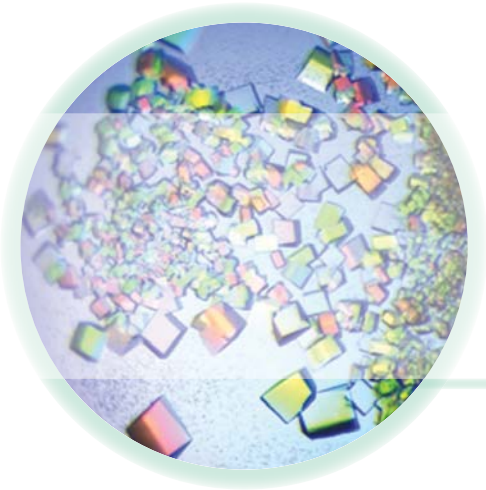
The programme has a notable application potential, namely in medicine. Insight into the preventive possibilities will impact the health and quality of life of large population subgroups. The recent clinical practice will be directly influenced by novel diagnostic approaches, with elucidation of a novel generation of biomarkers, preparation of newly designed diagnostic kits, and later with design of novel treatment modalities. The future of therapeutic interventions lies in personalized therapy; the application outputs of the research programme unequivocally accent this direction.

Research outcomes

- Clarification of molecular mechanisms of fertilization, identification of proteins and molecules of gametes and reproductive organs that are responsible for successful reproduction
- Development of antibodies against sperm and reproductive tract proteins crucial for successful fertilization and their commercialization
- New strategies in the treatment of autoimmune diseases in general
- Development of new anti-cancer substances and novel therapeutic approaches which will be transferred to the commercial sphere
- Identification of indicator genes for diabetes-specific heart abnormalities and genes contributing to developmental heart defects in diabetic embryopathy
- Early diagnosis, prevention and treatment of prenatal exposure to diabetes
- Identification of the genes participating in the development, function and disease of the liver which can influence the development of the metabolic syndrome
- Development of a new platform for biological studies based on single-cell expression profiling
- Description of the role of newly studied protein partners in modulation of phenotypic expression of diseases with a possibility to propose new therapeutic methods
- Preparation of prospective therapeutically used substances which can be transferred to the commercial sphere
- Identification of reliable biomarkers or develop a mass spectrometry-based therapeutic test







CORE FACILITIES

Guarantor: Jan Dohnálek
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Implementation of complex projects requires a high-quality methodological basis concentrated in the core facilities. Establishment of the following core facilities has been planned in BIOCEV, the first two as part of the European ESFRI infrastructure INFRAFRONTIER and Euro-BioImaging, Centre of Molecular Structure as an affiliated centre in European network INSTRUCT and the others as a top background namely for the Czech Republic. All will be open to external users to provide them with research services.

Czech Centre for Phenogenomics

will serve as a centre for the analysis of functions of individual genes using animal models. In particular, specific gene functions will be searched for and analysed and the data will serve to define the mechanisms controlling and inducing the disease development. The secondary goal will be search for novel therapeutic targets and new modalities for treatment of human diseases. In December 2009 already, the laboratory became part of European research infrastructure INFRAFRONTIER and will thus participate in gene research along with other top world centres of functional genomics.

Centre of Imaging Methods

is planned to serve as a national imaging facility. While the basic imaging methods will serve mostly the needs of BIOCEV researchers, the national importance will be connected with the recent techniques that reach the current technical limits for imaging molecules, cells and tissues. All the techniques of electron microscopy, light microscopy, and cytometry will form one unit optimally employing the unified technology and logistic environment. In 2010 BIOCEV joined the pan-European consortium Euro-BioImaging which will coordinate and organize various teaching activities on imaging and European access to the top imaging technology.

OMICS laboratory

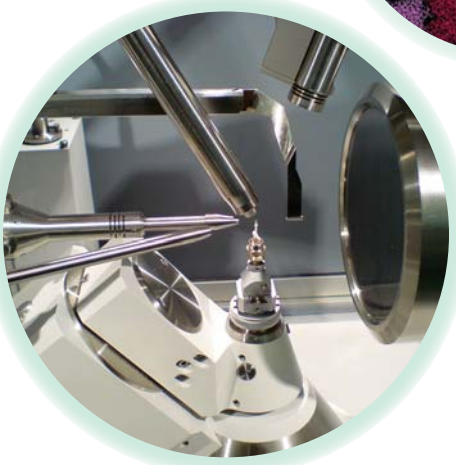
will focus on analysis of sequence and expression of DNA, RNA and proteins. Facility will provide DNA sequencing, genome-wide resequencing, transcriptomics and differential proteomics.

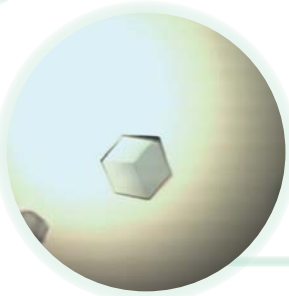
Centre of Molecular Structure

will encompass several laboratories providing a complex approach to studies of three-dimensional structure, function and biophysical properties of biological molecules. It will provide expertise, measurements and assistance in the following areas: crystallisation of biological molecules, single crystal x-ray diffraction, crystal structure solution, small angle x-ray scattering for determination of size and shape of molecules, infrared and, microcalorimetric techniques for monitoring of interactions and stability and determination of parameters of molecular interactions (SPR).

Cryotechnologies

core facility will be used for storage of cell lines, mouse sperm, embryos and other biological samples in liquid nitrogen or nitrogen vapour. The operation, diagnostics and maintenance of storage containers will be fully automated and controlled. The operating parameters of storage containers (temperature, humidity), and safety of the whole unit will be checked by a monitoring system with GSM and web interface outputs.





BIOCEV research topics

1. Functional Genomics
    - 1.1.1 Systematic Phenotyping of Mice and Rat Mutant Models for the Annotation of Gene Function
    - 1.1.2 Genetically Defined Mouse Models as a Tool for Studying Human Diseases
    - 1.1.3 Systematic Biological Approach towards Analysis of Complex Traits
    - 1.1.4 Insertional Mutageneses for the Characterization of Genes Participating in the Liver Function and Diseases
    - 1.1.5 Auditory Function in Mutant Mice
    - 1.1.6 Conditional Mice Mutants as Tools for Studying Genetic Disorders and Eye Physiology
    - 1.1.7 Lipocalins in Modulation of Mammalian Reproduction

2. Cellular Biology and Virology
    - 2.1 Eukaryotic Microbiology
        - 2.1.1 Biogenesis and Function of Cellular Organelles in Pathogenic Protozoa
        - 2.1.2 Mechanisms for Transport of Proteins through Mitochondrial and Bacterial Membranes
        - 2.1.3 Uptake and Intracellular Metabolism of Metals
        - 2.1.4 Genomics of Eukaryotes and Lateral Gene Transfer
        - 2.1.5 Molecular and Cellular Biology of Yeast Population, Interaction, Signalling and Differentiation
        - 2.1.6 Role of Metabolism, Signalling Molecules and Cellular Structures in the Process of Aging, Stress and Adaptation
        - 2.1.7 Transporters of Potassium in Regulation of the Cellular Cycle, pH and Response to the Stress of Lower Eukaryotes
        - 2.1.8 Virulence Factors of Yeasts
        - 2.1.9 Biological Activities of New Secondary Mold and Fungus Metabolites
    - 2.2 Biology of Cancer Cells
        - 2.2.1 Biochemical, Cellular and Molecular Biological Aspects of Cell Differentiation and Oncogenic Transformation Dependent on Proteases
        - 2.2.2 Cellular Functions of Plasma Membrane Proteases and Their Roles in Malignant Proliferation and Biology of Microbial Pathogens
        - 2.2.3 Molecular and Cellular Mechanisms of Invasiveness of Tumour Cells
        - 2.2.4 Interaction of Normal and Tumour-Altered Haematopoietic Stem Cells with Their Specific Microenvironment (Niche)

2.3 Virology
- 2.3.1 Interactions of Viral and Cellular Structures during Viral Infection
- 2.3.2 Development of Nanostructures for Medical and Veterinary Purposes Using Baculoviruses
- 2.3.3 Immunization against Tumours Caused by Human Viruses
- 2.3.4 Identification of Goals for Diagnostic and Therapy of Tumour Diseases Associated with Human Viruses
- 2.3.5 Study of Vaccinia Virus-Host Interactions

2.4 Structure and Differentiation of Mammalian Cells
- 2.4.1 Structures of the Cell Nucleus in gene Expression
- 2.4.2 Mechanisms Involved in Remodelling Chromatin Structure during Cell Fate Decision
- 2.4.3 Mitochondrial Structure and Gene Expression
- 2.4.4 Structure and Function of Membrane Receptors

3. Structural Biology and protein Engineering

3.1 Structure and Function of Biomolecules
- 3.1.1 Structure of Medically and Biotechnologically Important Enzymes
- 3.1.2 Structure of Molecules of Cell Signalling
- 3.1.3 Molecular Interactions of Anti-cancer Drugs
- 3.1.4 Structural Proteins and Their Complexes
- 3.1.5 Research of Natural Substances: Structure and Function
- 3.1.6 Intermolecular Recognition of Proteins and Nucleic Acids
- 3.1.7 Protein Structure Characterization by Advanced Mass Spectrometry
- 3.1.8 Research and Development of High-Affinity Binding Proteins

3.2 Bioinformatics and Molecular Modelling
- 3.2.1 Structural Bioinformatics of Proteins
- 3.2.2 Sequential Bioinformatics

4. Biomaterials and Tissue Engineering

4.1 The Development of Polymer Biomaterials and Tissue Engineering
- 4.1.1. Development of Polymer Therapeutics and Diagnostics for Treatment and Diagnostic of Cancer and Cardiovascular Diseases
- 4.1.2. Materials for Diagnostics and Biotechnological Processes
- 4.1.3. Polymeric Biomaterials for Regenerative Medicine
- 4.1.4. Bioartificial Structures for Replacement and Regeneration of Damaged Tissues

4.2. Cell Therapy and Tissue Replacement
    4.2.1. Application of Stem Cells and Biomaterials in Cell Therapy
    4.2.2. Stem Cells in Epidermis and their Application in Cell Therapy

5. Development of Diagnostic and Therapeutic Procedures
    5.1 Diagnostics of Cell Pathology and Molecular Therapy
        5.1.1 Diagnostics for Reproductive Medicine
        5.1.2 Immunomodulation of Autoimmune Diseases
        5.1.3 Molecular Therapy of Cancer
        5.1.4 Molecular Mechanisms in Diabetic Embryopathy
        5.1.5 Single-Cell Expression Profiling in Research and Diagnostics
    5.2 Molecular Basis of Human Diseases
        5.2.1 Molecular Pathology of Defects of the Heme and Hemoprotein Synthesis
        5.2.2 The Structure-Function Basis of Signalling with Gaseous Molecules
        5.2.3 Clinical Proteomics