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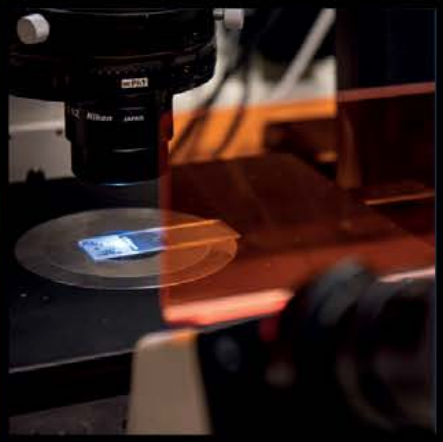
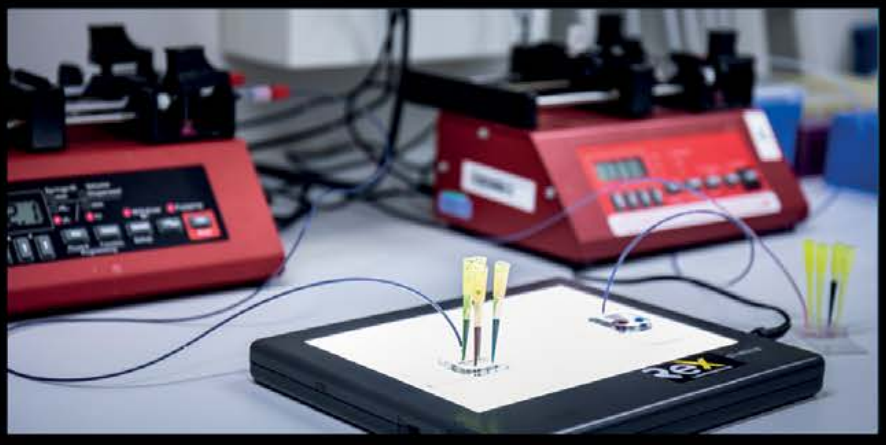


INSIDE THE BIOLOGICAL RESEARCH CENTRE, SZEGED



IMPRESSUM

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GREETINGS

In the course of nearly five decades of its existence, the Biological Research Centre, Szeged (BRC) has become an emblematic institution of Szeged and the Southern Great Plain Region, and has become a worldwide recognized research institution. The first laboratories of BRC were opened in 1971, then the completed and fully equipped institution was inaugurated in 1973. Having significant connections to Szeged, the world-famous Hungarian Nobel laureate, Albert Szent-Györgyi was a special guest of the opening ceremony. The founders of BRC intended to create a unique local research environment to improve the standards of basic scientific research, supervised by the Hungarian Academy of Sciences, aimed at reaching an internationally competitive level. In harmony with the mission of BRC, the multidisciplinary research activities were focused on four fields, including plant biology, biochemistry, genetics and biophysics, and were organized within the framework of four independent research institutes accordingly. The high standards of these research activities, the vibrant scientific atmosphere and the dynamism of the young research staff soon turned BRC into a flagship of Hungarian life science research, and the Institution gained international renown.

The year 2019 was a significant landmark for the Biological Research Centre, as well as for the entire research network of the Hungarian Academy of Sciences: the management of all academic research institutions was transferred to Eötvös Loránd Research Network, a newly established supervisory body. Since then, in line with international trends, BRC has paid particular attention to the social utilization of basic research findings, besides keeping its internationally competitive and acknowledged level of scientific research activities. Achievements of the past three years indicate that the organizational changes described above had a favourable effect on the quality and social recognition of the research conducted at BRC.

Photo taken at BRC on
11 October, 1973

NAGY, Ferenc
Director General of BRC

The present booklet aims to provide the Reader with an insight into the “secrets” of the research activities ongoing at BRC.

April 2023, Szeged

CONTENTS

INTRODUCING THE BIOLOGICAL RESEARCH CENTRE, SZEGED

The Biological Research Centre (BRC), founded in 1973, is **an eminent institution of internationally renowned Hungarian life science research**, and is one of the largest research institutions of the Eötvös Loránd Research Network in the field of life sciences. With approximately 260 scientists employed at BRC, the **scope of research activities cover all fields of modern biology**, including many domains of molecular and cell biology, the key issues of the industrial utilization of bacteria, controlled breeding of crop plants, as well as the most urgent challenges related to human health and environmental protection. While the Institutes of BRC **mainly host basic research**, the utilization of research findings is also in the focus of attention. Therefore, BRC scientists are active in the foundation and management of biotechnological companies, as well as in educational tasks. The efforts of the **worldwide known and acknowledged BRC research community** are hallmarked by a high number of international scientific publications and patents. The high research standards and outstanding achievements of BRC and its researchers have also been acknowledged by the European Molecular Biology Organization (EMBO), and in 2000 the European Union awarded BRC with the title of "Centre of Excellence of the European Union".

The Biological Research Centre hosts four Institutes corresponding to the fields of science studied (biophysics, biochemistry, genetics and plant biology).

The **Institute of Biophysics** is engaged in elucidating biological systems and basic biological processes from the molecular level to cells and tissues, using a physical approach. In addition to basic research, applied research in the fields of medical biology and biotechnology is also carried out. Modern physical procedures and methodologies are developed and utilized for these complex studies of biological systems.

The **Institute of Biochemistry** gained international renown in the 1970s upon studying restriction-modification systems capable of cleaving DNA with surgical precision, as well as upon characterizing the biological roles of lipids. In the 2000s the Institute's research profile was extended to include synthetic biology, evolutionary biology and systems biology. Classical biochemistry issues still feature among the research topics of the Institute, however, the most significant projects are those applying systems-level, high-throughput tests and computer-aided deep learning.

The **Institute of Genetics** aims at studying the processes related to ontogenesis, immunity, tumor development, DNA repair and autophagy (i.e. the process of breaking down and recycling abnormal or redundant proteins and cellular components produced during cell functioning), using various model organisms and molecular genetic methods.

The **Institute of Plant Biology** focuses on the identification and characterization of genes and molecular mechanisms responsible for light perception in plants, as well as those related to the utilization of light energy, plant development, stress responses and symbiotic interactions. For these studies model and crop plants, algae and cyanobacteria are used.

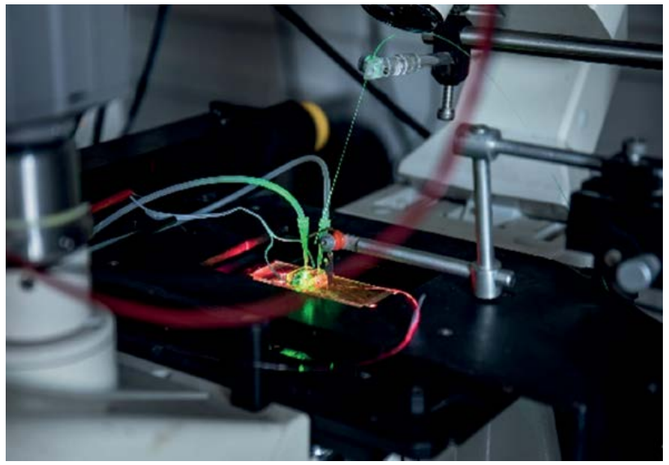
INSTITUTE OF BIOPHYSICS

BIOELECTRONICS, BIOPHOTONICS, „LAB ON A CHIP”

Investigation of biological interfaces. Basic physiological processes, such as biological energy and signal transduction, are related to transport processes through thin membranes that separate cells, organelles or organs, at different levels of hierarchy. They often involve the migration of electric charges, under the influence of electric field and voltage, therefore, the electric properties of biological interfaces (e.g. the frequency-dependent dielectric constant, surface charge density, resistance/conductivity) play an important role in these processes. Accordingly, our goal is to develop new experimental („lab-on-a-chip”) methods and theoretical models suitable for the investigation of physical (e.g. electric and optical) processes appearing at biological interfaces.

Integrated optical biosensors. Miniature electric and optical circuits enabling physical measurements, as well as the system of microfluidic channels, and thin, biocompatible substrate layers can be combined with proteins, living cells, and self-organized 3D cell cultures (organoids). This way, the so-called lab-on-a-chip techniques allow, for example, the complex biophysical examination of biological boundary layers that separate the organs of multicellular organisms. The controlling element of our integrated optical biosensors are made of a special, proteinaceous thin layer with nonlinear optical properties. These biosensors are suitable for highly sensitive detection of cell-surface or protein-protein interactions (e.g. antigen-antibody reaction), offering utilization in medical diagnostics.

Certain protein-based thin films can also be used as the active elements of integrated optical (IO) applications (e.g. ultrafast optical switches), due to their favorable optical properties. Our R&D work in this direction can contribute, in the long run, to the development of IO devices capable of fast and low-loss data transmission in telecommunication networks.



Integrated optical biosensor

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APPLICATIONS OF OPTICAL MICROMANIPULATION AND MICROFLUIDICS IN BIOPHYSICS

Studying cells using custom-made micro-tools. Understanding the functioning of single biomolecules (e.g. proteins) and the behavior of individual cells is at the forefront of biological research. In the last two decades, we played a significant role in developing novel photopolymerization techniques to create 3-dimensional microscopic tools comparable to the size of a cell. By using lasers and holographic optical tweezers to grab and drive these tools, we are able to probe the surface of living cells and measure the forces between biomolecules (e.g. receptors and their ligands).

Studying cells with microscopic systems of channels and chambers. Adaptation and evolution are fundamental processes in biology. To explore the underlying cellular and molecular mechanisms, we develop and apply new experimental methods to study individual cells and cell populations (e.g. bacteria) for extended periods. We fabricate complex microscopic systems of chambers and channels that serve as precisely engineered habitats for cells. These platforms are used to explore the effects of the microenvironment on single cells and cell populations, including changes in communication and adaptation mechanisms, motility, or antibiotic resistance. This enables us to investigate environment-induced evolutionary changes in the offsprings of single cells.

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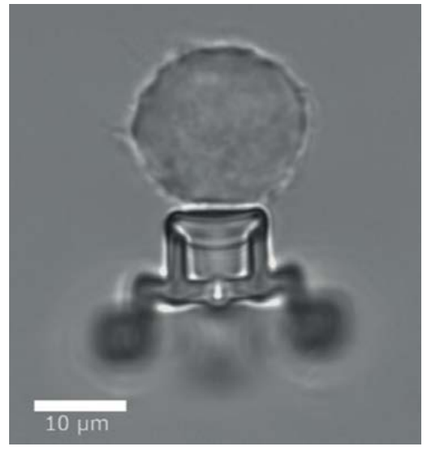
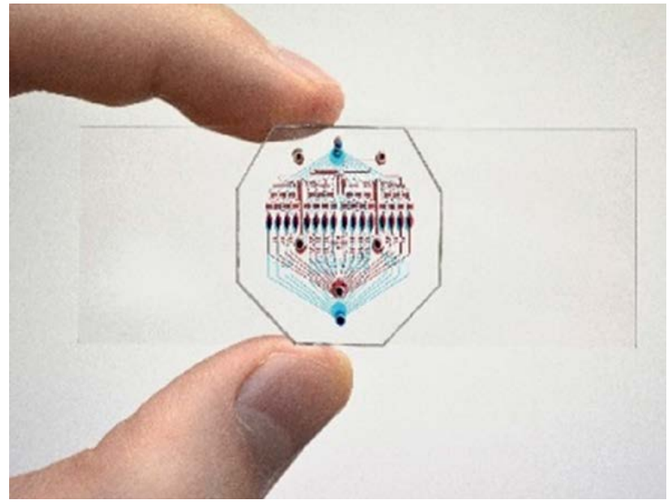
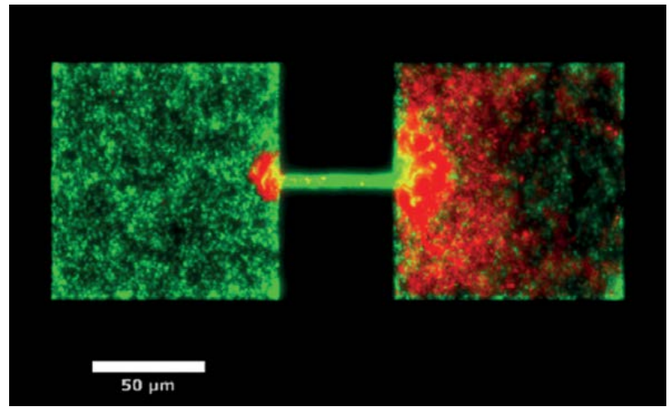


A living cell attached to a micromanipulation tool



Microfluidic chip



Interactions of bacterial populations in microscopic habitats

MOLECULAR FORCES AND MECHANICAL INTERACTIONS IN BIOLOGY

Microscopic mapping of intra-material forces and chemical composition. Mechanical interactions at the level of molecules, organelles and cells play crucial roles in the control of important physiological processes. Studying these mechanical interactions may yield valuable information about the functions of living materials. At this scale the atomic force microscope (AFM) is a powerful and versatile tool for the morphological characterization and measurements of intra-material forces. When AFM is combined with a Raman-spectrometer, the chemical characterization of biological materials at the microscopic scale offers a further outstanding opportunity. Good examples of their applications include the investigation of self-organization of short DNA or RNA molecules (oligonucleotides), morphological characterization of bacteria, mechanical examinations of red blood cells' elasticity, morphological and adhesion assessments of endothelial cells lining brain microcapillaries, or elastic characterization of tissue samples. As an outstanding application, the initial and crucial steps of the developement of brain metastases, i.e. tumor cells adhering to endothelial cells and crossing the endothelial layer, can be followed by AFM directly at high accuracy.

AFM-Raman microscope laboratory

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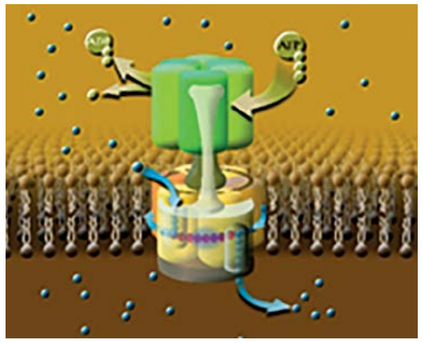
ENERGETICS AND DYNAMICS OF PROTEIN FUNCTIONS, AND MODELLING PROTEIN STRUCTURES

Structure determination of membrane proteins. The vacuolar proton-ATPase protein (V-ATPase), which can be considered as a molecular rotary engine that pumps protons (hydrogen ions), plays a crucial role in numerous physiological and pathological processes in eukaryotic cells. We have revealed that the activity of native V-ATPase in the natural membrane environment can be influenced by alternating electric field. At the same time, we were the first to determine the speed of rotation of this molecular motor, under near-natural conditions. The overall goal of our research group is to improve techniques for predicting the structure of membrane proteins, using a novel molecular biophysical approach based on spectroscopy and modelling, supplemented with machine learning methods.

Investigation of biological systems interacting with light. Numerous biological processes are triggered by or utilize the energy of light (e.g. photosynthesis). Partial emission of the absorbed energy in the form of fluorescence may yield information about the structure and dynamics of participating macromolecules. Our self-made instrument is capable of detecting the time evolution of fluorescence in the range of 100 femtoseconds to 10 nanoseconds, and covers the entire visible spectral window. Using this setup, we can also detect and follow the functions of proteins participating in electron transfer processes in real-time and with high accuracy. Utilizing the unique infrastructure available at the ELI-ALPS Research Institute in Szeged, and in collaboration with the University of Pécs and other research groups within the Biological Research Centre, we develop a novel workstation that will open new opportunities in the studies of ultrafast processes of light-utilizing biological systems.



Organization and function of the V-ATPase protein acting as a "molecular rotary engine"

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BIOTECHNOLOGY AT THE MOLECULAR AND CELLULAR LEVELS

Environmental protection, alternative fuels, bioremediation. For a sustainable life on earth, humanity must switch to circular economy, i.e. minimize raw material and energy consumption, as well as the emission of unusable and often harmful wastes. To achieve these goals, we apply traditional and new generation microbial and molecular biological techniques and biophysical methods. We build and study combined and well-designed communities (biomes) of microbes to produce alternative fuels. In the field of bioremediation (biodegradation), we have developed numerous biotechnological approaches to dispose of dangerous substances, oil derivatives and drug residues. We pay special attention to the resuscitation and activation of viable but not culturable (VBNC) microbes for environmental applications.

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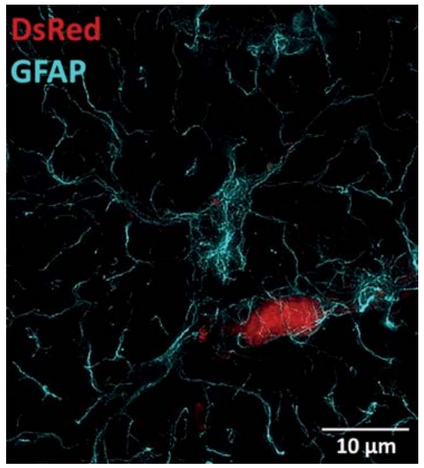
STRUCTURE, FUNCTIONS AND PATHOLOGIES OF THE NEUROVASCULAR UNIT

Brain metastases, aging, inflammation: the role of brain microvessels. Although the human brain constitutes only 2 percent of the total weight of our body, this organ demands 20 percent of resting oxygen and energy consumption. The connection between the brain tissue and blood circulation, which ensures its energy supply, is provided by the neurovascular unit. The most important biological functions of the neurovascular unit include forming an active interface between the circulation and the brain (blood-brain barrier) and ensuring blood supply, in accordance with the requirements of neural activity (neurovascular coupling). The neurovascular unit plays an important role in the development of various neurological disorders, such as stroke, brain traumas, tumors, and neurodegenerative diseases, and is highly involved in processes related to aging. Our research group examines the mechanisms that are essential for two key steps of the formation of brain metastases: the passage of tumor cells through the blood-brain barrier, and the initial survival of tumor cells in the brain microenvironment. Our goal is to better understand the communication between tumor cells and cells composing the neurovascular unit, which is essential for the



Super-resolution (STED) microscopic image of the cells composing the neurovascular unit

development of effective prevention and therapeutic strategies. Taking advantage of the opportunities provided by molecular biology and advanced microscopy techniques, we execute *in vitro* and *in vivo* studies to elucidate the roles of different cell types of the neurovascular unit in aging and in the development of inflammatory processes.

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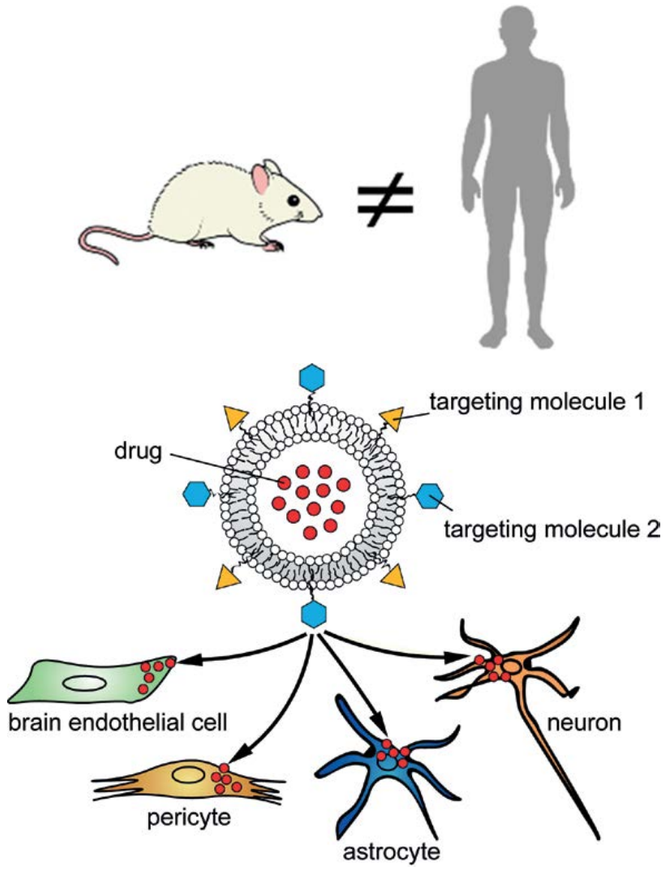

Drug delivery into different cell types by targeted nanoparticles

BIOLOGICAL BARRIERS

Modelling the protective biological barriers of organs, targeted drug delivery. Biological barriers protect the organisms from the surrounding environment. They also separate important organs, like the brain, from systemic blood circulation to provide a special environment for their functioning. However, the same processes that provide protection for the brain tissue, make the entry of drugs into the central nervous system challenging. In-depth investigations of biological barriers, including the intestinal, respiratory and corneal epithelium, as well as brain capillaries (the so-called blood-brain barrier) contributes to a better understanding of their structure and functions, and thereby supports the development of more effective therapeutic approaches for diseases related to barrier dysfunctions. Also, these studies contribute to improving targeted drug delivery.

Our group focuses on various pathological conditions related to the dysfunctions of biological barriers, including Alzheimer's disease, epilepsy, acute pancreatitis and obesity. Since experimental animals are not universally suitable to study human diseases, we aim to create more appropriate research models of human biological barriers. For this purpose we have established a new generation of barrier models with the use of human cells and microelectronic and microfluidic chip devices, by taking advantage of the interdisciplinary approach in our Institute. We have successfully designed and investigated targeted nanoparticles for drug delivery across barriers, capable of cell entry. Encapsulation of bioactive molecules into nanoparticles functionalized with targeting ligands to enhance penetration across biological barriers significantly improves the efficiency of drug delivery.

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NEURONAL PLASTICITY

Assessing the cellular and molecular pathways of neurodegenerative disorders and developing novel therapeutic strategies. Neuronal plasticity is a special mechanism of the nervous system that allows the neuronal tissue to rapidly adapt to environmental changes. Furthermore, this phenomenon is essential for learning processes, as well as for regeneration after acute or chronic nerve damage. When the capacity of neuronal plasticity is exhausted, cellular destruction of the nervous system is initiated, and the first signs and symptoms of neurological diseases appear. Most of these neurodegenerative disorders involve different brain regions and have distinct phenotypes, however, the primary cellular and molecular mechanisms underlying the process of degeneration are quite similar. Our research focuses on amyotrophic lateral sclerosis (ALS), a progressive and incurable neurodegenerative disorder characterized by the loss of motor neurons in the spinal cord and brain. Since the nerve terminals of the affected motor neurons are located in the innervated muscles, this disease allows us to collect samples of damaged neurons without ethically questionable biopsy from the brain of ALS patients. By studying the axon terminals of these affected neurons, we also get an insight into the pathomechanisms of other neurological disorders, since the primary machinery of degeneration is overlapping in numerous neurological diseases. Moreover, such human samples acquired by muscle biopsy are comparable to samples from experimental animals, therefore, the goodness of animal models is easily verified. The fundamental goal of our research is to identify and understand the primary degenerative events in ALS. Furthermore, we aim to develop novel preclinical therapeutic strategies of neuroprotective and neurodegenerative potentials to protect the healthy nervous system and to alleviate the degenerative events of the diseased nervous system, via maintaining and restoring neuronal plasticity and homeostasis.

Quote from an ALS patient: "Not ALS , but hopelessness kills us." Our group's mission is to give hope to these patients

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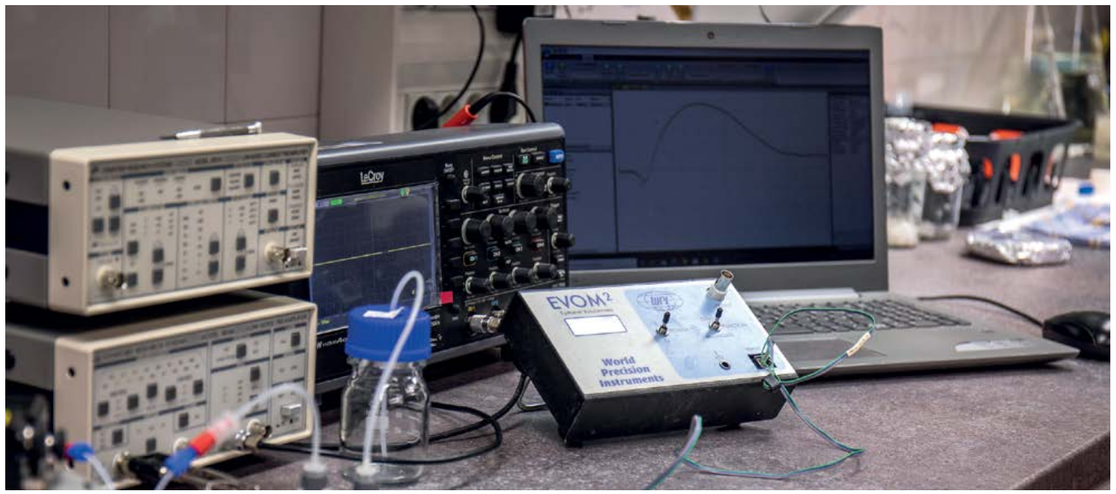

INSTITUTE OF BIOCHEMISTRY

EUKARYOTIC MOLECULAR BIOLOGY

Cell cycle regulation. Cells are the smallest living units of organisms. Constant, but controlled cell proliferation is essential for the development of an individual, as well as for the physiological functioning of all tissues and organs. Cell division and its preliminary processes are collectively termed cell cycle. It is an extremely precisely regulated process, and its defects may lead to severe diseases such as tumor formation. The cell cycle is regulated by a large number of proteins, which can be „switched” on and off, i.e. activated in order to perform their function and inactivated when the process is done. Activation and inactivation are mediated by temporary chemical changes, including phosphorylation. One of the main areas of our research involves the kinase enzymes which add phosphate groups to proteins regulating the cell cycle, as well as phosphatases that remove these phosphate groups. A better understanding of their functions and interrelations has theoretical significance in biology, and may also have an outstanding practical impact, as it may promote research into clarifying the pathomechanisms involved in developmental disorders and malignant cell proliferation. Thereby, it may also establish new approaches to the treatment of these pathologies.

Computer-generated fantasy drawing of lymphocytes, a type of white blood cells (illustration)

Mass spectrometry, protein identification and regulatory networks. Mass spectrometry is an indispensable analytical technique in the investigation of proteins, which is a core issue in modern molecular biology. It enables the identification and characterization of hundreds or thousands of proteins isolated from a biological sample, shedding light on the protein composition in different cell types, and their qualitative and quantitative changes upon certain stimuli. Such qualitative changes include e.g. phosphorylation, acetylation, glycosylation or the attachment of lipid anchors to the proteins. These modifications can largely influence the localization, structure or function of a protein, as well as its interactions with other protein molecules. Deciphering the relationship between these structural changes and their molecular functions will enlighten the regulatory network of proteins, and thus it would allow a more predictable intervention in certain biological processes.

Tumor immunology. Although cell cycle regulation quite often gets impaired in our body, the resulting loss of control over cell proliferation does not necessarily give rise to malignancies, which may be surprising. This beneficial phenomenon is due to our immune system, as numerous protective mechanisms involved in the innate and acquired immunity work together to destroy these overproliferating cells before they grow to form detectable tumors. A better understanding of these immune functions and their possible modulations may help to establish new approaches to prevent tumor formation.

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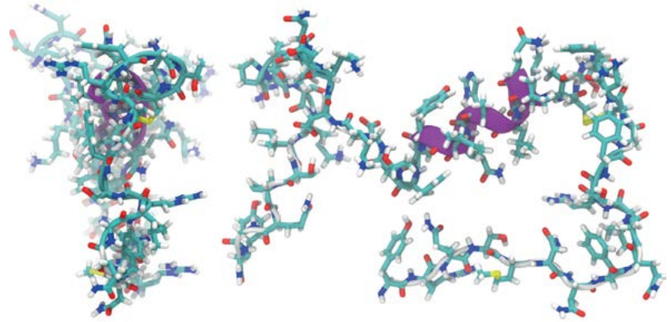
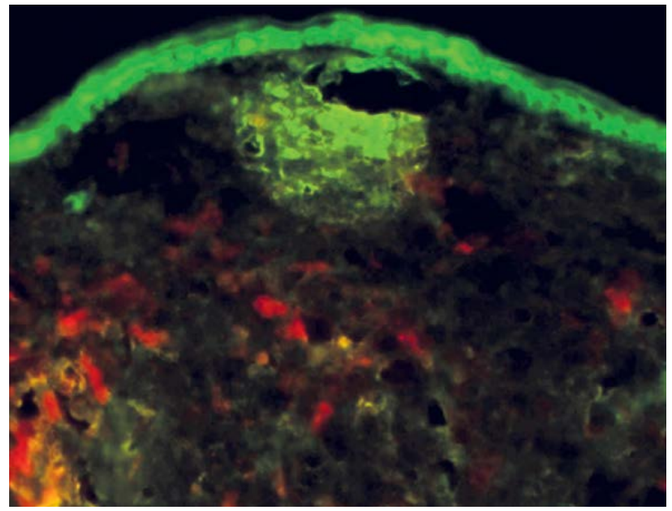
NEUROBIOLOGY

Receptor research. Signal transduction, i.e. the process of transferring biological information from cells to cells, including neurons, involves small molecules. These molecules are released from the cells in which they are produced, and bound to receptors on target cells. Receptors are proteins, usually located on the cell surface. When these signalling small molecules (so-called ligands) are bound to the receptor, a biological signal is generated and travels in the cytoplasm, or induces a detectable change in the potential (voltage) of the cell membrane. Receptors are of particular importance not only for physiological signalling, but also for therapeutic interventions, as the majority of currently applied drugs bound to cellular receptors to produce their therapeutic effects. The main objective of receptor studies is to elucidate the underlying principles of ligand-receptor binding and receptor functioning. The first step usually includes receptor-ligand experiments carried out *in vitro* (in test tubes in the laboratory). Based on these results and supporting literature data, computer models of receptor functions are developed. Ideally, these computer models are appropriate to design and develop new drug molecules, whose effectiveness may and must be verified in further experiments. In our Institute ligands labelled with isotopes or fluorophores (fluorescent chemical compounds that can be induced to emit light), as well as ligands with non-natural composition are produced in-house, sometimes using novel synthetic chemical methods elaborated for the given purpose.



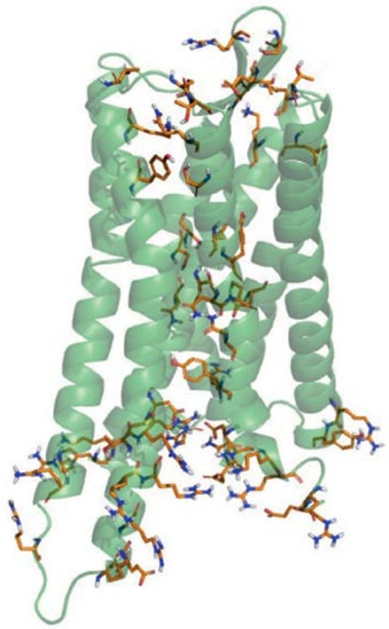
A ball-and-stick model of protein fragments (peptides) (illustration)



Microscopic section of the ear of a mouse expressing the Thy1-YFP fusion protein, 7 days after injecting 4T1 type tumor cells which express the red tdTomato fluorescent protein (Jósvay *et al.*, *Sci Rep* 4:6776). (Courtesy of Creative Commons Attribution-NonCommercialNoDerivs 4.0 License, reproduced with permission.)

Our research mainly focuses on opioid and cannabinoid receptors. The former bind opiate analgesics and illicit drugs, whereas the latter bind endocannabinoids and cannabis derivatives (hashish, marijuana); both are located on the cell surface. These research areas are justified by the alarming spread of illicit drug use, strongly associated with the opiate crisis of the 21st century in Western countries. A better understanding of ligand binding characteristics, activation, regulation and signal transduction pathways of these receptors may contribute to the development of advanced analgesics with

Intravenous drug user (illustration)



Three-dimensional structure of the mu opioid receptor (Mitra *et al.*, *Biomolecule* 11:670). (Courtesy of Creative Commons Attribution 4.0 International License, reproduced with permission.)

less or no adverse effects, as well as more effective treatment approaches for drug addiction.

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STRESS BIOLOGY

The role of lipids in stress response. The state of balance required for the proper functioning of an organism (homeostasis) can be disturbed by external stimuli. These stimuli are often called stressors, and the resulting phenomenon is called stress. The central role of proteins in the molecular mechanisms involved in stress response has long been recognized, while the roles of lipids (fatty and oily compounds) are still to be explored in this field. Lipids are the main components of biological membranes, including the cell membrane and the membranes encapsulating intracellular organelles. Presumably, they have an important function in several elements of the stress response. For example, fluidity (i.e. the extent of flowability) of membranes may be a sensitive marker of environmental factors (e.g. of temperature). Similarly, changes in the lipid composition of membranes is an important mechanism involved in the cellular adaptation to variations in environmental conditions. In our Institute, ultrasensitive methods of high temporal and spatial resolution (e.g. image-based fluorescence-correlation spectroscopy, single-molecule microscopy, high space resolution lipidomics) are applied to study the roles of biological membranes in stress responses. Using cell-based and animal models we study how stress response mechanisms can be modulated in order to control pathological immune responses, as well as the pathologies behind malignant and neurodegenerative diseases or metabolic disorders. In addition to a better understanding of these processes, research into lipid-related stress response mechanisms may reveal new perspectives of membrane-lipid based therapeutic approaches, and thus may contribute to the treatment of dyslipidaemias (disorders of lipid metabolism), as well as to an improved management of human, animal and plant health issues related to climate change.

Gene editing. Certain diseases, especially those of genetic origin, might only be treated via gene modifications, including the proper correction or partial modification of defective DNA sequences. The genetic material (genome) of living bacterial cells has long been modified with varying success; however, in eukaryotic cells the majority of these techniques do not work or are seriously hindered. Introduction of the CRISPR/Cas system, considered as the “Swiss Army Knife” of genetic engineering has brought a revolutionary breakthrough in this field. This system works like a pair of “molecular scissors”, appropriate to cleave the genome at almost any positions in a controlled fashion. However, unfortunately, targeting is often imperfect, and a mismatch in DNA cleavage would be more harmful than beneficial in case of a potential therapeutic application. An improved system known as high fidelity (hi-fi) CRISPR/Cas mutant nuclease is definitely more precise, however, the higher fidelity in DNA cleavage is inherently associated with lower efficiency (i.e. the probability of cleaving the target gene at the proper position is decreased). To resolve this issue, we are developing a series of CRISPR/Cas systems which can be classified according to their efficiency and fidelity. This series may offer a particular nuclease for any individual target genes to be cleaved with the highest possible efficiency, at the cost of minimal inaccuracy (i.e. the particular CRISPR/Cas variant is the least likely to cleave DNA at locations other than the target position). The practical applicability of these systems is tested on various cellular disease models in our laboratory, in order to simulate and establish the expected future use of CRISPR/Cas systems in gene therapy.

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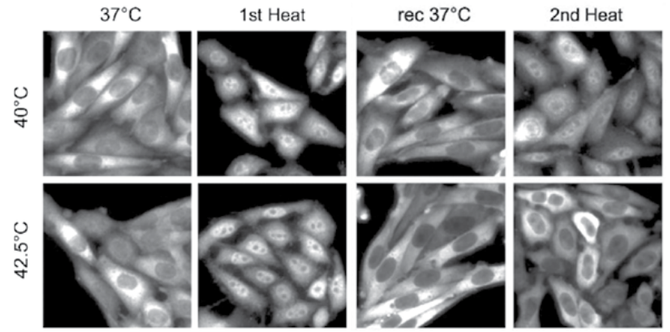
SYNTHETIC AND SYSTEMS BIOLOGY

Evolution biology. We all have learnt about evolution, however, it is less known that evolution can be modelled in a test tube (*in vitro*). For this purpose we use microorganisms (bacteria and fungi), as they may divide as often as every 20 minutes under ideal conditions, thus detectable changes may develop in a cell

Everyday stress (illustration)



Distribution of heat shock protein hsp25 in Chinese hamster ovary cells after two doses of heat shock (Peksel *et al.*, *Sci. rep.* 7:15643) (Courtesy of Creative Commons Attribution 4.0 International License, reproduced with permission.)

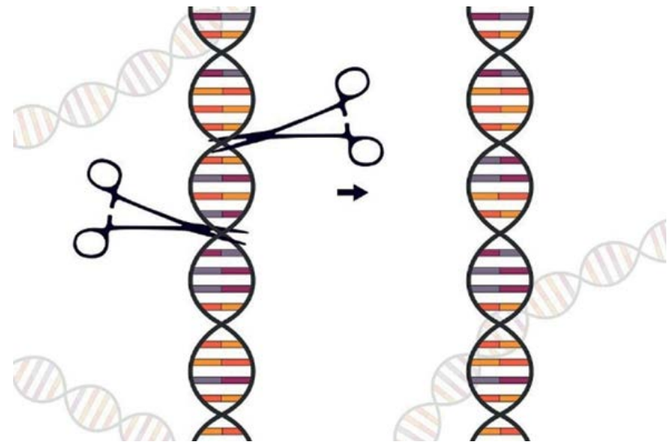
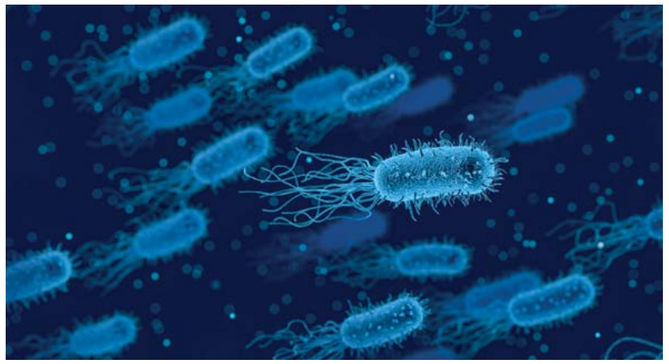


Illustration of the “molecular scissors” for gene edition



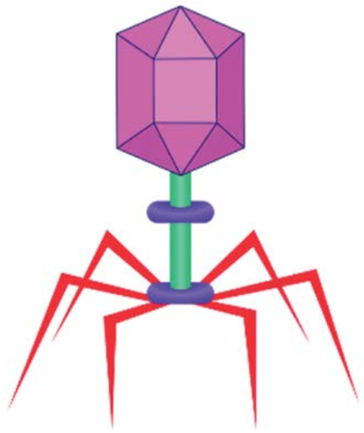
Computer graphics of the bacterium species *Escherichia coli* (illustration)

Fruiting bodies of *Coprinopsis cinerea* (grey shag) in a Petri dish

line within a few days, in contrast to real life evolutionary processes that may take much longer, from years (e.g. antibiotic resistance) to several hundred thousands or million years (e.g. development of a new species). What kind of changes are to be expected in evolution studies? Any detectable changes may appear, however, the most important phenomena are changes in visual appearance (phenotype) or in metabolic processes, as well as the development of antibiotic resistance. The significance of antibiotic resistance is well known, and we all understand how dangerous it is when a bacterial infection (e.g. pneumonia) cannot be cured because the pathogen is resistant to antibiotics. Via elucidating fundamental biological processes, our research helps to predict bacterial resistance evolution to various antibiotics, thus our findings support the development of novel antimicrobials that are expected to be more efficient than currently available agents.

Bacteriophage research for therapeutic purposes. Antibiotics are not the only means of fighting against bacterial infections. Alike humans, bacteria can be infected by viruses that may even kill them. These viruses, called bacteriophages, have been used to treat certain bacterial infections for a century. Our research aims to develop specific approaches for a faster, safer and more predictable utilization of phages in clinical practice. To this end we have developed and apply novel gene editing methods in our laboratory.

Microscopy-based single-cell analysis, characterization of individual cells. All research activities described above necessitate that we are capable of executing rapid and precise microscopic examinations of bacterial, animal or human cells in a high-throughput manner. The scale of these studies can be immensely improved by automating the evaluation of the plethora of microscopic images obtained, by utilizing well-trained computer algorithms. Our novel image analysis techniques build on deep learning, a specific machine learning approach, which highly increases the capacity and accuracy of microscopic image analyses. Moreover, our unique microscopy system is capable of extracting single-cells of interest from the sample by a robotic technology, and these individual cells are submitted to detailed biochemical characterization to reveal changes of potential pathological significance.



Schematic drawing of a typical bacteriophage (illustration)

Systems immunology. Adequate functioning of our immune system is essential for a successful defense against microorganisms (bacteria, viruses) or to protect against cancer. Adaptive immunity involves the specific immune responses activated against a given pathogen or tumor cells. Although the immune recognition process eliciting immune responses is highly complex, its general principles can be identified. The *Systems Immunology Group* aims to explore these principles for a better understanding of the adaptive immune mechanisms evoked by pathogens and tumor cells. Our research is focused on the human leukocyte antigen (HLA) molecules which are responsible for the regulation of the immune system via differentiating between self and non-self. To this end, HLAs present antigens (characteristic molecules) on the surface of “dangerous” cells. Extreme diversity of HLA molecules practically exclude the possibility that two individuals carry exactly the same set of variants. Therefore, immune recognition exhibits genetically determined, individual differences, which may predispose to or protect against certain diseases. Elucidating the role of individual HLA variants in the development of various diseases would be a valuable support to personalized medicine.

Microscopic image analysis (illustration)

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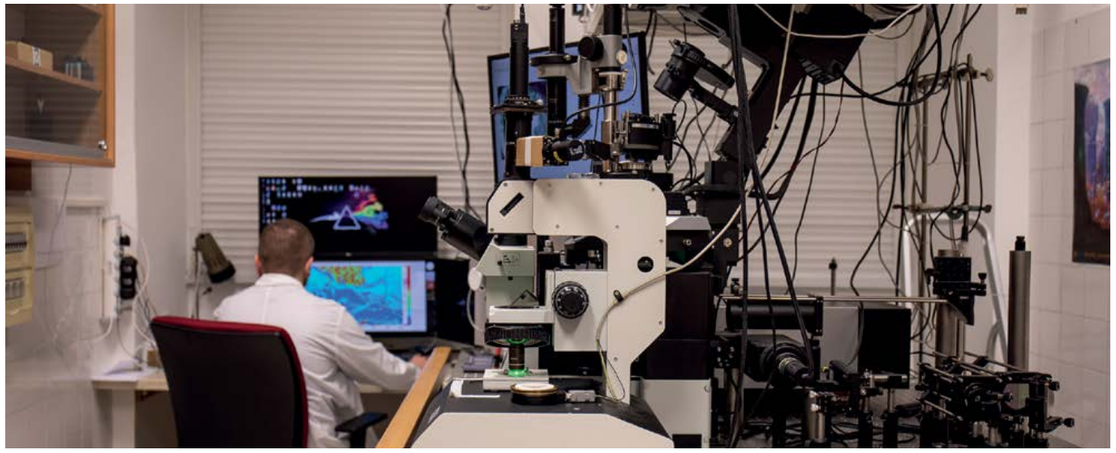
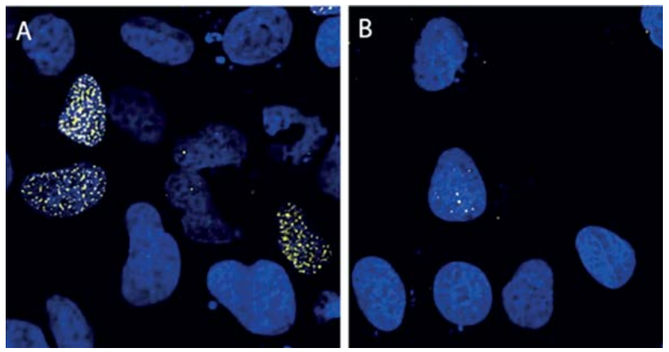


INSTITUTE OF GENETICS

GENOME INSTABILITY AND CARCINOGENESIS

Genome instability and carcinogenesis, drug resistance in tumors. The genome, also called genetic material or hereditary substance stored in the cell's nucleus, is the complete set of information specific to an organism. As the genome is passed from cell to cell and generation to generation, genome stability is key to individual health and to the survival of species. However, this hereditary material is subject to a wide variety of damaging (mutagenic) effects which can cause genetic diseases. Therefore, maintaining genome stability is an essential and continuous task in the body, so a complex system of repair mechanisms has evolved to fulfil this role. Dysfunctions of these so-called DNA repair systems lead to genome instability, resulting in higher mutation frequency and, consequently, an increased risk of developing genetic diseases.



Sites of DNA damage repair appear as yellow dots in the figure. **(A)** Yellow fluorescence indicates the binding of proteins involved in DNA damage repair. **(B)** Mutant protein variants result in abnormal binding, indicated by decreased fluorescence intensity

It is also well-known that mutations are the most important factors in cancer development. A wide array of tumorigenic mutations are described, and the main biological pathways involved in tumorigenesis have long been in the focus of intensive scientific research. Besides using traditional anti-cancer agents (cytostatics), targeted therapy with drugs that specifically target abnormal proteins transcribed from altered genes are an integral part of patient care nowadays, regarded as a breakthrough in cancer therapy. However, in most cases, the main obstacle to complete remission and cure is the development of various resistance mechanisms within the tumor tissues, both against conventional and targeted therapies. The main reason for resistance development is the emergence in malfunctions of DNA repair systems within tumor cells, leading to accelerated genome changes and consequent adaptation to therapy.

The *Genome Instability and Carcinogenesis Unit* aims to elucidate the molecular mechanisms involved in drug resistance and recurrence of tumors, in order to facilitate the establishment of new diagnostic and therapeutic approaches. We actively investigate the proteins that promote copying damaged or altered (e.g. by chemotherapy) genetic material and the regulatory mechanisms of these processes. We aim to explore the factors that determine whether error-free or mutation-prone replication mechanisms are activated in the cell cycle process. An important focus of our research is screening for potential drug molecules (so-called small molecules) capable to modify DNA repair systems, and thus may have the potential to reduce the probability of resistance evolution associated with accelerated mutagenesis.

Additional mechanisms of tumor development and resistance evolution. Increased activity of certain DNA elements, including LINE1 retrotransposons present in the human genome, play an important role in the accelerated induction of new mutations in tumor cells. Our unit investigates the regulation of transposons' functioning and the role of this process in the pathogenesis of cancer. We aim to develop a specific system to measure the activity of LINE1 retrotransposons.

In addition to the well-known double helix structure, DNA has a variety of newly discovered secondary molecular structures. The so-called G-quadruplex structures are involved in the regulation of genome functions. As a new focus area, our unit investigates how G-quadruplex structures affect the process of DNA duplication and thereby genome stability.

Double strands of DNA are bound to so-called histone and non-histone proteins. This complex is called chromatin. The regulatory function of chromatin's structure is of particular importance in DNA damage repair. Our unit investigates the role of gene mutations that lead to reduced efficacy of and resistance to PARP inhibitors, a class of anti-cancer drugs acting on the chromatin. Our findings may support the development of new tumor diagnostic procedures, and thereby may be utilized in clinical practice or in the development of novel anti-cancer agents.

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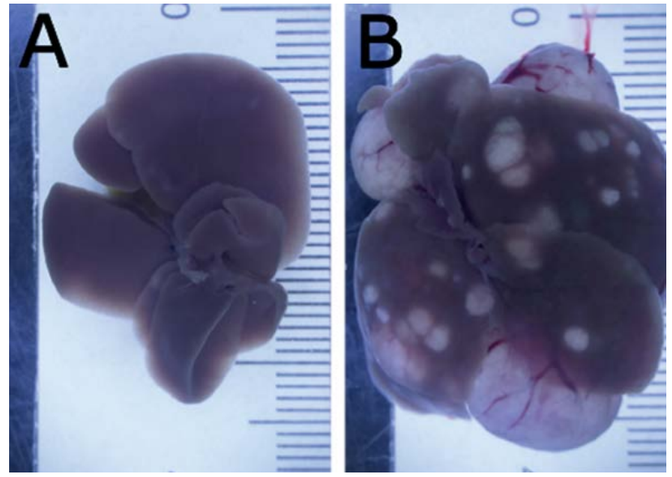
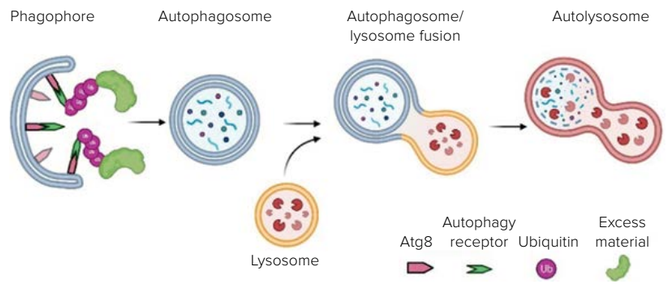


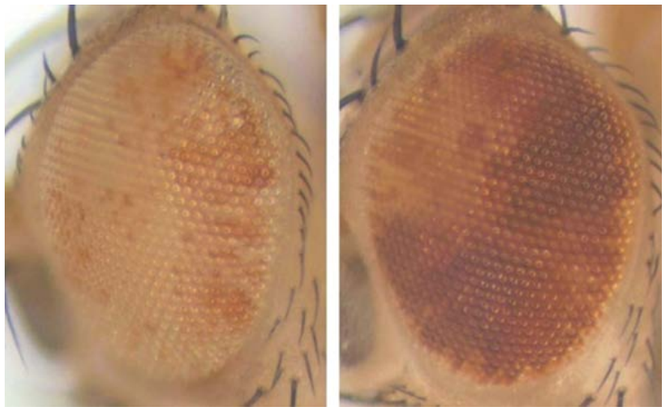
Inducing liver tumors in mice by generating a combination of mutations known to cause cancer. **(A)** Healthy mouse liver. **(B)** Mutations induce massive liver tumor growth

DEVELOPMENTAL GENETICS

Studies of developmental genetics on fruit fly. The past twenty-five years of genetic research can definitely be regarded as the era of genome programmes. These genome programmes have focused on mapping the entire genomes of thousands of species, including humans, leading to the revolutionary achievement of complete sequencing of the human genome. Based on these results, comparative studies of species were also carried out. These studies indicate that the structures, as well as the number and functions of genes in different genomes show significant similarities, even across large phylogenetic scales. Therefore, experimental animals are appropriate to model human genetic diseases (animal models), and the knowledge gained can be successfully applied in medicine.

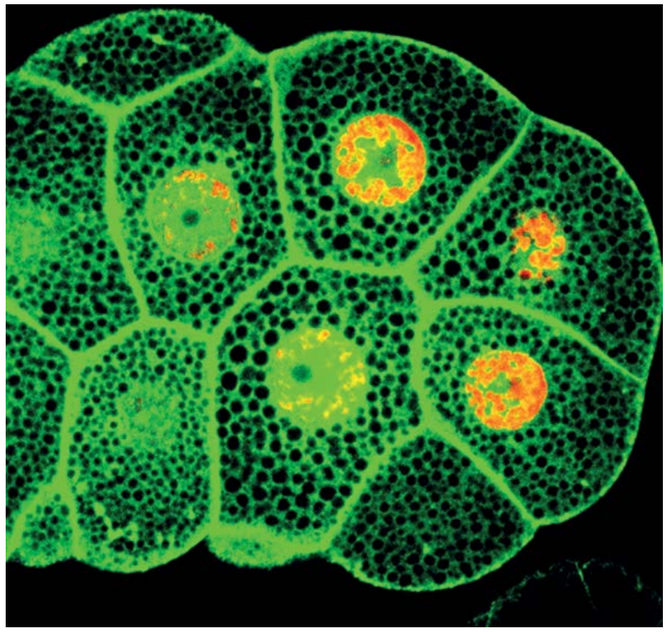


During autophagy, excess material is wrapped in membranes within the cells. The resulting particles fuse with the cell's acidic degradation centres called lysosomes, where these excess materials are broken down into reusable components



The effects of heterochromatinization factors can be assessed *in vivo* in animal models via the expression of the gene that causes red eye colour in *Drosophila melanogaster*

For example, the genome of fruit fly (*Drosophila melanogaster*), the most popular genetic model organism, contains 70 percent of the genes known to be responsible for human diseases. Thereby, authentic *Drosophila* models of human diseases can be developed to investigate their genetic background and develop potential new treatment strategies against them.



Actin filaments and the actin-binding protein mysosin (labelled in green) are present in the salivary glands' nuclei of *Drosophila* larvae, allowing to study the effects of actin on gene expression

The strategic research objective of the *Developmental Genetics Unit* is to investigate basic developmental genetic phenomena in the model organism *Drosophila melanogaster* and in mammalian cell cultures. As a key aspect, we aim to transfer our basic research results and established technical developments into human medicine. Therefore, we develop authentic *Drosophila* and mammalian cell models of human diseases to screen for potential drug candidates and investigate the pathophysiological background of these disorders. Our unit is the intellectual heir to the Insect Genetics Group, established in 1971, whose research scope has recently been extended with a specialized stem cell-based experimental system (called human induced pluripotent stem cell-based technique).

Modelling neurodegenerative diseases. Autophagy is the process of breaking down and recycling abnormal or redundant proteins and cellular components (cell organelles) produced during cell functioning (see the figure on previous page). This process is similar in humans and model organisms.

Defects in autophagy may result in abnormal accumulation of proteins and cell organelles, which often manifest as neurological diseases in humans. Our research aims to develop the *Drosophila* models of single-gene-regulated (monogenic) rare neurodegenerative diseases linked to autophagy-mediated degradation, to thoroughly study these pathologies.

Relationship between chromatin-level gene regulation and tumor formation. Chromatin-level gene regulation enables the regulation of genes, gene clusters, or even entire chromosome regions by the modification of a chromosome's structure. Defects in chromatin-level regulation lead to severe human diseases such as tumor formation. Our unit uses a *Drosophila* model and mammalian cell lines to investigate the so-called heterochromatinization factors responsible for the formation of a closed chromosome structure and the proteins responsible for its maintenance.

Diverse cellular roles of actin. Actin filaments play a crucial role in changes of cellular shape, motility of cell organelles, and muscle contractions. Defects in the structure and function of actin filaments are typically associated with muscle or nerve dysfunctions. Studying the actin cytoskeleton in *Drosophila* models aims to elucidate its effects on gene expression. Also, we aim to get a better understanding of the factors that regulate the function of this actin cytoskeleton. In addition, our unit investigates the developmental biological processes that direct how the actin-based scaffold of muscle and nerve cells is generated, and aim to explore the cell biological roles of nuclear actin. Furthermore, we aim to develop *Drosophila* models of human neurodegenerative diseases.

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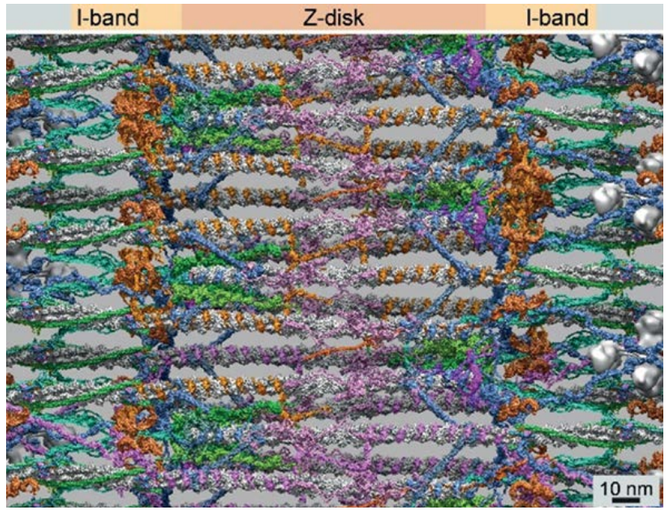
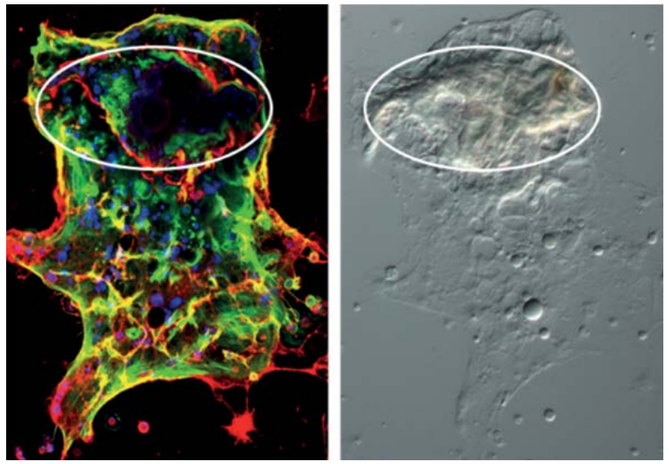


Sarcomere is the structural and functional unit of muscles. It is characterized by exceptional molecular arrangement. Muscle strength results from the summation of molecular forces arising between actin filaments and actin-binding proteins in the sarcomere

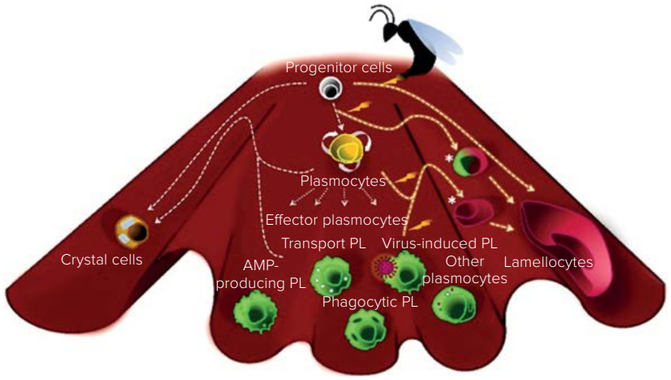
IMMUNOLOGY

Living organisms exist in a highly complex biological environment, which includes a large variety of bacteria, viruses, and fungal pathogens. Fighting against pathogens is a constant challenge for all creatures. In animals and humans, innate (inherited) immunity, the ancient type of defence against pathogens, serves as the first-line defence mechanism. It is activated as soon as an 'invader' is detected. Fruit fly (*Drosophila melanogaster*) is a universal model animal for the intensive research on innate immunity. The genetic background for the development and functioning of immune cells in *Drosophila melanogaster* is highly similar to that of the immune regulatory systems of higher-order species of animals and humans. The *Immunology Unit* uses *Drosophila* model systems to investigate the development and conversions (transdifferentiation) of blood cells that compose the immune system of fruit fly.

Genomics and proteomics based approaches are employed to investigate the defence strategies of specific insect groups, including certain *Drosophila* species, that are exceptionally effective in fighting against pathogens. We aim to reveal the molecular mechanisms related to these specific defence strategies. In fact, we have discovered a multi-nucleated giant blood cell type that plays a key role in the immune defence of fruit fly, alike some toxin genes of bacterial origin incorporated into the genome of *Drosophila* species. Our experiments aim to identify the specific molecules that play a crucial role in immune defence against pathogens. These molecular entities may serve as a basis for drug development to support the efforts targeted at fighting against human pathogens.

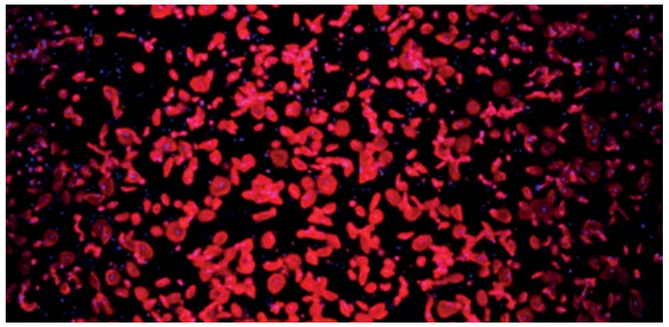


Multinucleated giant blood cells surround and kill pathogens



Possible pathways of blood cell maturation in the larvae of fruit fly. The cells responsible for defence against parasitoid wasps are formed from progenitor cells, as well as from functional engulfing cells (PL, plasmocyte)

Our interest is focused on the development and maturation of blood cells that serve as the immune system of fruit fly. Alike human blood cells, these blood cells of fruit fly proliferate and mature in specific sites of the body, namely in haematopoietic organs and tissues. One of these organs is the lymph gland of *Drosophila* larvae, which contains haematopoietic stem cells and functions as a blood-cell-producing tissue, similarly to the red bone marrow in vertebrates. Our research has identified specific genes that play an important role in the maintenance of blood-cell-producing stem cells. These genes are also found in mammalian cells, and defects of these genes are frequently associated with cancers, such as leukaemia. Currently, our experiments are aimed at elucidating the molecular functions of the proteins encoded by these genes, and other related processes.



Blood cells of hopTum mutant *Drosophila* larvae with a leukaemia-like phenotype. Increased blood cell proliferation and transdifferentiation is detectable in hopTum larvae. During transdifferentiation, a significant proportion of engulfing cells are transformed into encapsulating cells, marked in red by antibody staining

In recent years, an interesting phenomenon has been reported. Namely, when a family of parasitoid wasps called ichneumon wasps or ichneumonids lay their eggs into the larvae of fruit flies, the blood cells that engulf bacteria are transformed into encapsulating cells that kill the developing wasp larvae. Similar transformation processes have also been observed in mammalian immune cells. This transformation is probably essential for our immune system to quickly adapt to various challenges, with relatively little energy consumption. To study this transformation process revealed in fruit fly larvae, we have developed a novel methodology which is applicable to maintain blood cells in cell cultures, and monitor their transformation in real-time via video microscopy. A machine learning-based image analysis technique is utilized to analyze these microscopic images, which enables us to distinguish between different cell stages.

Moreover, our unit investigates innate immunity in a mammalian model. Macrophages are highly variable cellular components of the innate immune system. They are involved in defence against pathogens, as well as in the initiation and suppression of inflammation, and in regenerative processes. The complex molecular microenvironment influences the expression of genes that control macrophage functions in many ways, which essentially determines the functional characteristics of macrophages. Our unit investigates the different macrophage states that result from the interactions of various microenvironmental signals and the genes they activate. Also, we aim to explore transcriptional memory in a mouse model, using a combination of transcriptomic, epigenomic, and immunological methods.

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INSTITUTE OF PLANT BIOLOGY

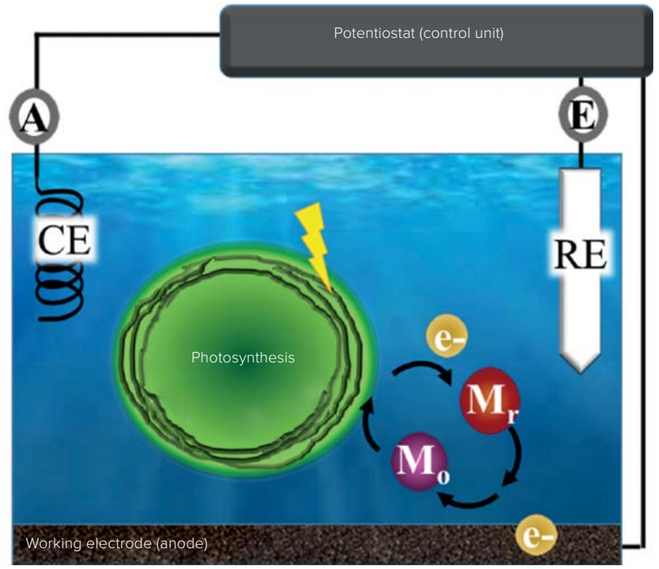
PHOTOSYNTHESIS RESEARCH FOR THE ENHANCEMENT OF PLANT PRODUCTIVITY AND FOR THE DEVELOPMENT OF RENEWABLE ENERGY RESOURCES

Photosynthesis research with regard to sustainability. Life on Earth is sustained by solar energy stockpiled by photosynthesis, which therefore plays a decisive role in the evolution of our global environment. Photosynthesis research is gaining increasing importance in counteracting the negative consequences of climatic change with regard to sustainable food production and generating renewable energy.

Our research aims to elucidate the molecular mechanisms that determine the initial steps of photosynthetic conversion of light energy. Moreover, we focus on elaborating the conversion of solar energy into fuel or electric energy, and aim to enhance plant productivity by increasing the efficiency of photosynthesis.

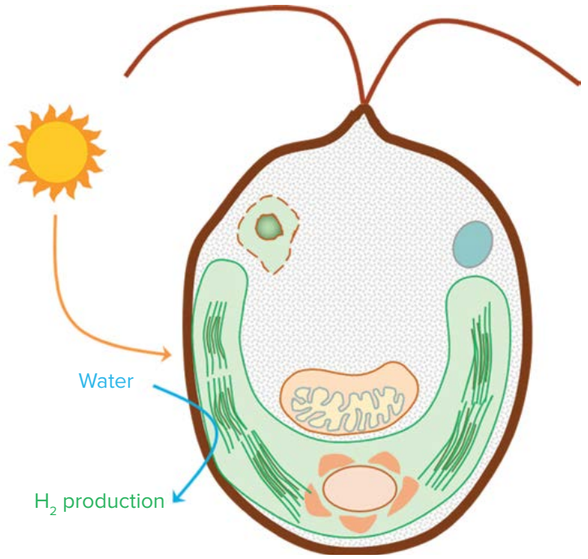
It is well-known that excitation energy of solar radiation is highly efficiently transferred from light-harvesting complexes to photochemical reaction centres; however, details of the exact molecular background of this process and its regulation are to be elucidated. We study these pathways by state-of-the-art, ultrafast optical spectroscopic methods, supplemented with atomic-level structural information, and work in co-operation with the ELI-ALPS laser centre (Szeged) and international partners.

Biohybrid light energy converting devices. Photosynthetic organisms can be utilized to generate electricity. Devices capable to convert light energy by utilizing algal cells or isolated photosynthetic reaction centres have made tremendous progress over the past decade; however, their industrial application still necessitates further development. Our research aims to enhance the performance of these photosynthetic power-generating devices by means of biochemical, molecular biological and electronic methods.



Scheme of direct electric power generation using algae

Renewable energy production using algae. Green algae generate hydrogen as a by-product of photosynthesis, and this hydrogen is a promising source of renewable energy. We have developed a methodology, protected by a European patent, which allows continuous hydrogen production by *Chlamydomonas reinhardtii* algal cells, based on photosynthetic water splitting under natural light conditions. Our research goal is to further enhance the efficiency of this process. Also, we aim to design and construct a photobioreactor that could be the prototype of a large-scale algae-based hydrogen-generating system.



Scheme of hydrogen production using algae

REGULATION OF PLANT GROWTH AND ADAPTATION TO THE ENVIRONMENT

Adaptation and stress tolerance at the molecular level. Our research focuses on understanding the ontogenesis and stress tolerance of plants and their adaptation to the environment at the molecular level, with regard to practical applicability of our findings. In addition to their significance as basic research, these issues also have economic relevance, since they may contribute to breeding new varieties with improved yield and stress tolerance. These are especially timely requirements, because climate change inducing extreme temperatures and uneven distribution of precipitation may generate increasingly challenging conditions that will not only affect natural vegetation, but will also reduce the efficiency of plant production.

Research focusing on counteracting the negative effects of climate change. Enhancing the efficiency of photosynthesis and selecting plant species with improved stress tolerance may play an important role in alleviating the adverse effects of climate change. In Hungary the plant 'energy willow' (*Salix viminalis Gigantea*) is an important subject for research in this field. We have provided evidence that duplication of the genome size of energy willow enhances photosynthetic efficiency, carbon dioxide uptake, salt tolerance, as well as the amount of organic material generated in biological processes (biomass).

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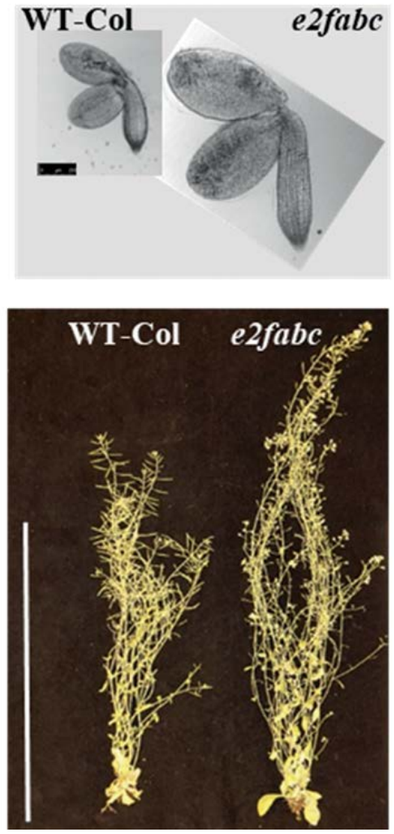
Controlled enhancement of plant size and crop yield. Plants' ontogenesis depends on the function of a plant-specific tissue type, the so-called meristem (dividing tissue) which produces new cells in the developing plant. This process is controlled by a dedicated regulatory system. Our research has revealed that inactivation of a group of genes involved in this regulatory system results in the development of larger embryos (ovulum or preliminary seeds) and larger plant organs. Currently we study whether this regulatory system is general to the plant kingdom, and whether its modification may contribute to increasing plant size and crop yields.

Crop yield may also be enhanced by plant treatment with microalgae (containing bioactive compounds) or their active extracts, added to plants either as a medium or a nutrient. These bioactive agents stimulate plant growth and increase stress tolerance. Since the effects of microalgae on plant development are underexplored, we study the potential fields of application of microalgae isolated from Hungarian waters, and aim to elucidate the molecular background of their effects using various model and crop plants.

The role of light and the biological clock in plants' life. The adaptation of plants to environmental conditions starts with the perception of environmental stimuli, primarily of light and heat. These factors play a fundamental role in the regulation of plant development. Signal transduction pathways activated by photoreceptors modify gene expression according to actual light and heat conditions, thereby promote adaptation to the environment. We have developed an experimental system appropriate to determine the functions and interactions of individual photoreceptors, as well as their role in the regulation of plant growth and flowering. Alike in animals and humans, the circadian rhythm of plants enables adaptation to the cycles of days and nights. Our research focuses on studying the relationship between light stimuli and plant circadian rhythm. We aim to elucidate the biological role of formerly unknown regulatory factors of circadian rhythm identified by our group.

Protective molecules induced by environmental stress. Environmental stress alters the metabolic processes of plants, leading to the accumulation of antioxidants and other protective molecules, such as ascorbic acid (vitamin C) and proline. Our research aims at a better understanding and targeted modification of ascorbic acid metabolism, as well as the exploration of the associations of drought and salt stresses with photosynthetic processes.

Plant "quality control systems" and genome editing. Normal genetic functioning requires the identification and removal of defective gene products, such as inadequately edited mRNA molecules or proteins with structural defects. Degradation of defective gene products is carried out by cellular "quality control systems". We assume that the proportion of defective gene products is significantly increased under stress conditions. Thus, we study the role of plant "quality control systems" in response to stress, and attempt to enhance the efficiency of nitrogen fixation naturally executed via the symbiotic interaction of plants and root colonizing bacteria. To achieve this, we focus on targeted modifications of these mechanisms.



Growth enhancement by modification of growth-controlling molecular mechanisms in *Arabidopsis* plants

Genome editing is an important tool in modern plant biology research. This technique enables targeted modifications of various metabolic and stress-induced protective processes. Site-specific modifications of the genetic material (genome), called oligonucleotide-directed mutagenesis (ODM), yield controlled mutations of target genes, using short DNA molecules (oligonucleotides) tailored to the chemical structure (sequence) of the specific gene(s) of interest. This intervention allows the improvement of plant traits without inserting foreign gene(s) into the genome.

Building on world-class prominent infrastructural background. Available at the Biological Research Centre, outstanding plant fenotyping systems enabling automated monitoring of the development of plants and their responses to environmental effects provide a world-class prominent infrastructural background for research addressing the adaptability of plants. Similar fenotyping

systems for studying microalgae are under development.

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Automated plant fenotyping system monitoring the growth and physiological states of plants

INTERKINGDOM INTERACTIONS OF PLANTS, ALGAE AND BACTERIA, AND THEIR BIOTECHNOLOGICAL UTILIZATIONS

The majority of organisms live in complex communities, whose members establish interactions of various types and intensities with one other. We aim to elucidate the interactions existing in natural and synthetic communities at the molecular level, in order to provide scientific findings of practical applicability that may offer solutions for the societal challenges of our era.

Fixation of atmospheric nitrogen. An extremely important trait of leguminous plants is their capability to form nitrogen-fixing symbiosis with *Rhizobium* bacteria. Thereby, the nitrogen content of soil is increased, which reduces the demand for fertilizers manufactured using excessive fossil energy. The specificity and efficiency of the interaction of plants and *Rhizobium* bacteria are maintained by interspecies communication via chemical compounds. Such molecules include, for example, plant flavonoids, bacterial nodulation (Nod) factors, the cell surface polysaccharides of *Rhizobia* and, in certain cases, nodule-specific, cysteine-rich (NCR) peptides of the host plant.

These NCR peptides, discovered in our laboratory, mediate the transition of *Rhizobia* into an endosymbiotic nitrogen-fixing form. These so-called bacteroids are much larger and more efficient than those associated with plants not producing NCR peptides, and lose their viability outside of the nodule. Our research aims at a better understanding of the functions of NCR peptides, in order to increase the nitrogen-fixing capability of those leguminous plants in which this irreversible (terminal) differentiation of *Rhizobia* is missing under normal conditions. Elucidating these mechanisms would significantly contribute to efforts focused at increasing the amount of biologically produced biomass and, consequently, it would support the improvement of food safety and the reduction of the use of nitrogen-containing fertilizers produced at excessive fossil energy demands.

Antibacterial proteins. NCR peptides have another special characteristic: those with positive charges have antibacterial properties against a wide range of bacteria. We aim to elucidate the mechanisms of action behind this antibacterial effect, and study the applicability of these NCR peptides and their derivatives for the development of antibiotics with a novel mechanism of action.

Environmental protection using algae. Interactions within complex communities may also be exploited in order to improve the efficiency of green algae-based biohydrogen production. Our findings have confirmed that the respiratory activity of bacteria sharing the natural environment of algae significantly contributes to the utilization of oxygen molecules produced by photosynthesis. Thereby, it contributes to maintaining the conditions necessary for the proper functioning of hydrogenase enzymes, and thus it helps to increase the efficiency of hydrogen production. Consequently, an important direction of research into algal-bacterial interactions focuses on the utilization of natural and synthetic algal-bacterial communities for photosynthetic hydrogen production.

Algal-bacterial communities are also employed for wastewater treatment. They are efficient tools to remove the residual nitrogen and phosphorus content of traditionally treated wastewater. In addition, algae may be used for desalinization of wastewaters of high salt content, due to their capability of photosynthetic biomass production and great stress adaptation.

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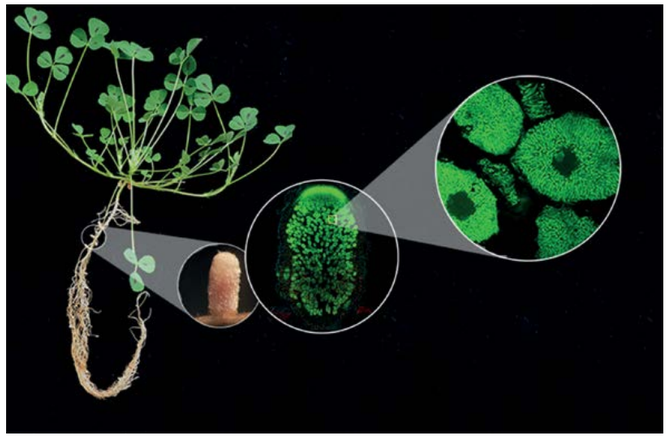
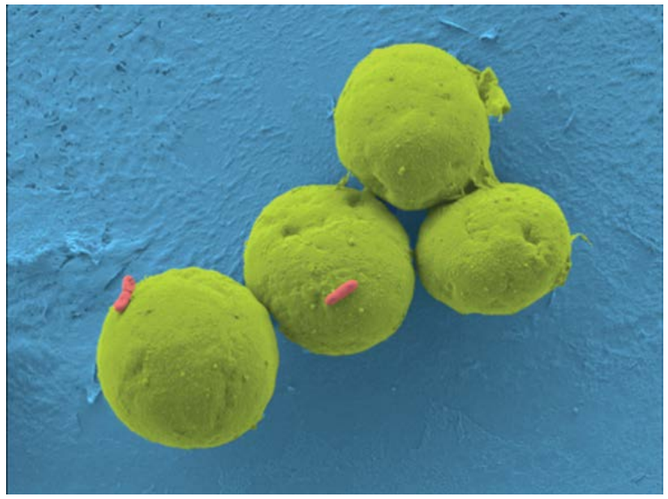


Symbiotic *Rhizobium* bacteria developing on the roots of leguminous plants are capable of fixing atmospheric nitrogen



Interaction between green algae and bacteria

ALGAL-BACTERIAL INTERACTIONS, HYDROGEN PRODUCTION, WASTEWATER TREATMENT:
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THE BIOLOGICAL RESEARCH CENTRE IN NUMBERS

5
significant industrial projects per year

3
outstanding international grants per year

42
years, the average age of the R&D staff

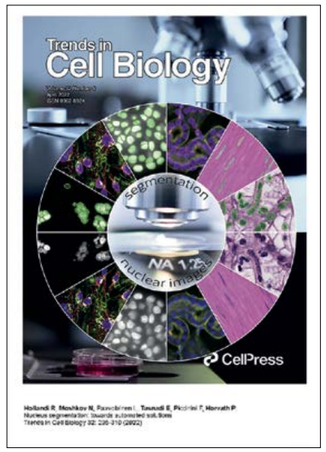
200–250
scientific publications per year

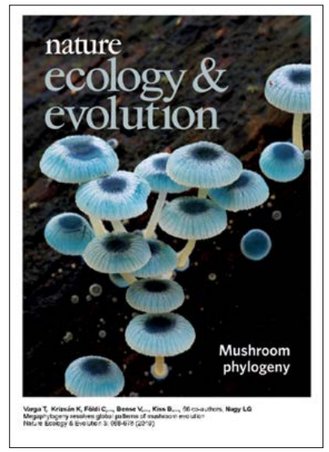
100–110
mentored undergraduate students per year

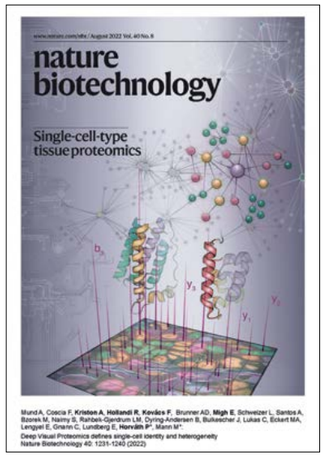
70–80
PhD students per year

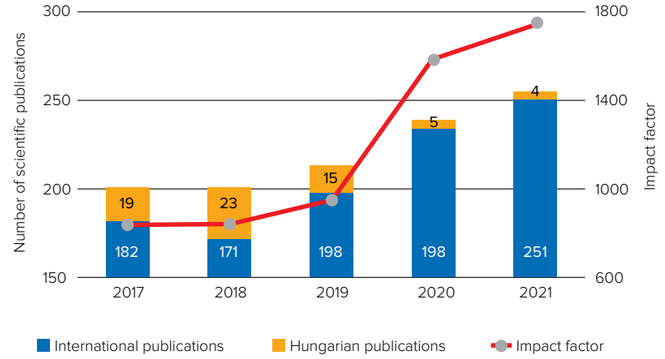
SCIENTIFIC PUBLICATIONS

The mission of the Biological Research Centre is to perform high-quality exploratory research in various fields of molecular and cell biology, and publish the results in prestigious scientific journals. As a quality indicator, our research papers are regularly accepted for publication in the most distinguished scientific journals of the world. The overwhelming majority of our publications qualifies as Q1/D1. This means that 70–75% of our research papers were published in the highest quarter of the most acknowledged 1,000 journals of the relevant discipline (Q1), whereas 40–45% of all papers were published in periodicals included in the top 10 (D1). In average, 2 of 200–250 publications per year are highlighted on the front page of the particular journal as featured articles.









Impact factor (IF) is a scientometric index that indicates the relative importance and quality of scientific journals. It is calculated on the basis of the number of citations received by the articles published in the given journal in a well-defined period of time.

Publication activity of BRC scientists in the past 5 years (2017–2021)

MAIN PROJECTS INVOLVING BRC

HCEMM

The **Hungarian Centre of Excellence for Molecular Medicine** (HCEMM) was established with support from the European Union's Horizon 2020 research and innovation programme. The HCEMM scientific strategy, building on molecular medicine-based approaches, aims to provide a **better understanding of the molecular pathomechanisms** behind immuno-inflammatory diseases, metabolic and cardiovascular diseases, genomic instability and cancer, as well as infections of bacterial, fungal or viral origin and related co-morbidities. The fundamental objective of the research programme is to **promote the diagnostics, management and prevention** of these high-burden disorders. High-end technologies available at the advanced core facilities support prominent and internationally competitive scientific research.

EnergUP

The EU-funded EnergUP project aims to **find innovative solutions for clean energy production in order to slow climate change**. Photovoltaic cells that utilize the photosynthetic properties of algae are considered an ideal candidate to convert light into electric current. The EnergUP project aims to sizeably improve the efficiency of algae-based photovoltaic devices, making them a good choice for climate-neutral, clean energy production.

MULTICELLULARITY

The EU-funded research on the evolution of multicellularity focuses on fungi as a model system to **elucidate the genetic basis of the convergent evolution of multicellularity and that of organismal complexity**. It tests the hypothesis that besides modifications of protein-coding genes (e.g. gene duplications), changes to non-coding DNA segments, including cis-regulatory elements and gene expression patterns (including protein isoforms) have significantly contributed to the evolution of complex multicellularity (differentiated 3-dimensional structures).

discovAIR

The international research project, discovAIR focuses on **discovering the Cellular Landscape of the Airways and Lung Tissue** by mapping the unique characteristics of the wide array of cell types composing the lung, and elaborating the way these cells communicate in healthy and diseased individuals. To achieve this, discovAIR will **create an Atlas of the Human Lung**, a 3D reconstruction of lung tissue architecture. As another important objective, it aims to identify how the specific properties of different cell types change from a healthy to a diseased state, such as in chronic obstructive pulmonary disease (COPD) or asthma.

FAIR-CHARM

The EU-funded FAIR CHARM project builds on two complementary imaging solutions, SWIM and SLIDE, to capture the biological processes, as well as the cellular and extracellular structures involved in disease onset and progression, in real-time. **A better understanding of biological systems and processes** opens up new opportunities for the **development of novel therapeutic strategies**.

RESISTANCE EVOLUTION

The EU-funded project focuses on studying the **bacterial evolution of resistance against antimicrobial peptides (AMPs) and associated collateral sensitivity**. Collateral sensitivity is a biological phenomenon in microorganisms when evolution of resistance towards a single drug is accompanied by an increase in sensitivity to other antimicrobial agents.

AwARE

The EU-funded AwARE project aims to **identify and develop novel antibiotics that are resistant or at least less prone to the emergence of drug resistance**. Using a recently developed technology (DIvERGE), an efficient and comprehensive screening of resistance evolution against potential drug candidates is executed to reveal the probability of chemical and metagenomic changes expected to evolve in clinically relevant pathogens. Applying these screens at an early stage of the drug development pipeline, their results provide a valuable support to identify drug candidates less prone to resistance evolution. Thus, it offers the possibility to **focus on drug developments that may provide antimicrobial agents with long-term effectiveness in clinical practice**.

ALAGAE4IBD

Algae are valuable biological resources of an array of natural compounds that can relieve pain and inflammation. ALGAE4IBD, an EU-funded research initiative, focuses on under- and unexplored algae to **identify novel compounds with pain-relieving and anti-inflammatory activities**. Specifically, it aims to develop novel therapeutic agents for the prevention and treatment of inflammatory bowel disease (IBD).

NATIONAL LABORATORY OF BIOTECHNOLOGY

Under the leadership of the Ministry of Innovation and Technology (ITM), 18 National Laboratories were established in Hungary in 2020, related to 4 areas as follows: 'Industry and Digitalization', 'Culture and Family', 'Health', and 'Secure Society and Environment'. The National Laboratory of Biotechnology, led by the BRC, aims to utilize advanced biotechnology systems and achievements to **develop unique and innovative approaches and therapeutic solutions in various health-related fields**. Specifically, designing and developing novel antimicrobial agents and searching for therapeutic bacteriophages are in the focus of the pillar of **fighting against antibiotic resistance**. The other main focus area is aimed at **developing an mRNA vaccine against the African swine fever virus** (ASFV), responsible for huge losses in animal husbandry. The third pillar focuses on the high-throughput screens of approved medications to find potentially new application areas related to the **unmet need of treating rare genetic disorders**.

NATIONAL LABORATORY FOR PHARMACEUTICAL RESEARCH AND DEVELOPMENT (PHARMALAB)

The National Laboratory for Pharmaceutical Research and Development (PharmaLab) is a member of a consortium, and operates in collaboration with small and middle enterprises and large industrial partners. Its outstanding research and development (R&D) activities are aimed at 4 focus areas. The first **pillar of molecular oncology** focuses on the development of novel targeted anticancer agents. The **pillar of neuropharmacology** is engaged in biomarker research aimed at neurodegenerative diseases and inflammatory neurological disorders. The **pillar of biotechnology** aims at the development of DNA/RNA and proteomics-based diagnostic and therapeutic antibodies to improve the diagnostics and management of pandemic infections, cancers and autoimmune diseases. Semi-industrial manufacturing of the identified antibodies is also under development. The last **pillar of pharmaceutical technology development** aims to elaborate novel innovative approaches for drug development and manufacturing to improve the competitiveness of the pharmaceutical industry.

SYMBIOTICS

In agriculture, nitrogen fertilizers provide the nitrogen source required for plant growth. Limiting the use of nitrogen fertilizers is a priority public issue to reduce the energy consumption associated with their manufacturing, as well as their detrimental environmental effects, including greenhouse effect and soil/water pollution. As a possible solution, **biological nitrogen fixation** (BNF) is being considered. The process of BNF is most efficient in the symbiotic interaction between leguminous plants and *Rhizobium* bacteria, although the exact level of the efficiency of nitrogen fixation depends on the plant species involved. For example, BNF is highly efficient in alfalfa, while it is less efficient in

the soy plant. This difference is mainly explained by the specific peptides produced in the symbiotic cells of alfalfa, missing in the soybean plant. Thus, transferring these specific peptides into other species may serve as an effective tool to **enhance the efficiency of biological nitrogen fixation**. Moreover, the vast majority of these peptides may also serve as potential drug candidates to tackle antimicrobial resistance, as no resistance mechanisms are known to evolve against these molecules. Furthermore, as these peptides are non-toxic to humans or animals, they could be appropriate for human use, as well as for use in animal husbandry or agriculture. The research program was launched with support from the European Research Council (ERC), and is now supported by the 'Frontline Excellence Programme' ('Élvonal') of the National Research, Development and Innovation Office of Hungary.

NATIONAL LABORATORY OF AGRICULTURAL BIOTECHNOLOGY AND PRECISION BREEDING FOR FOOD SAFETY

The consortial project focuses on agricultural technology and precision breeding for food safety, under the umbrella of the Agrotechnology National Laboratory. It aims to **improve well-balanced and secure agricultural production**, as well as to **enhance healthy and quality foodstuff production**. The high-quality expertise and the unique infrastructural background of the consortium members provide a solid basis for state-of-the-art scientific research focused to find solutions for the complex agricultural challenges of our era.

ARTIFICIAL INTELLIGENCE BASED SINGLE-CELL ANALYSIS

The project, illustrated by the phrase "***From basic research to clinical practice***", builds on the single-cell analysis concept and a multi-omics platform to **elucidate the cellular and molecular processes involved in physiological functioning of human organs and tissues**, as well as to **characterize pathologies of single-cell origin**. This world-class prominent single-cell analysis technology utilizes deep-learning, a specific subset of machine learning and artificial intelligence, and it is capable to **identify even the most minute differences in human samples**. **Individual cells** with evidence of any changes indicating possible pathologies **can be extracted from the sample by a pioneering technique, and are subjected to molecular analyses**. The final aim of the research project is to implement these approaches into clinical practice, in order to **provide the most effective tailored therapy for each patient**, based on the identified molecular pathologies driving disease processes.

"INVESTING INTO OUR FUTURE"

The Hungarian co-operational research project focuses on **molecular phenotyping** related to **chronic inflammatory airway diseases** (including chronic obstructive pulmonary disease, asthma and cystic fibrosis) and to **SARS-CoV-2 coronary virus infection**. In the former group of airway diseases molecular phenotyping helps to elucidate the exact pathology, which is of therapeutic significance. Various forms (phenotypes) of these chronic inflammatory airway disorders are characterized by a wide spectrum of cellular processes and mediators, strongly associated with the natural course and the progression of the particular disease, as well as with the frequency of acute exacerbations. **Regarding SARS-CoV-2 coronary virus infection**, achievements of this molecular phenotyping research, executed at BRC, **may revolutionize patient management via predicting the expected course of the disease**. The research project aims to identify blood biomarkers applicable to predict the cytokine storm associated with life-threatening Covid-19 infection or pneumonia of both lungs resulting in respiratory failure.

ESTABLISHING AN INNOVATIVE MULTI-OMICS DIAGNOSTIC PLATFORM

The research project, supported by Hungarian grants, aims to establish an **innovative multi-omics diagnostic platform to support the precise diagnosis and treatment of women with infertility of unknown origin**. The research aims to establish a **pioneering treatment strategy** that provides a sophisticated approach to elucidate the pathologies behind infertility, allowing effective, patient-tailored management. This innovative strategy builds on systems-level diagnostics that regards the human body as a network, and analyzes the complex system of the interactions of lipids, metabolites, proteins and genes. Based on these findings, holistic treatment approaches are developed.

NKP ELI

NKP ELI is a collaborative research project involving the ELI ALPS Laser Research Institute, the Biological Research Centre and the University of Pécs. Its main objectives include the **development of a femtobiology workstation** and **studying light-induced biological processes** using spectroscopy with few-cycle pulses. Research findings are expected to answer fundamental questions in photobiology, via giving insight into and providing a better understanding of the process of energy transfer between photosynthetic light-harvesting complexes and reaction centres, as well as regarding the functioning of plant-derived photoreceptor proteins.

NAP-3

Three research groups of BRC are involved in the 3rd term of the National Brain Research Program (NAP) of Hungary.

The 'Lendület' Microscopic Image Analysis and Machine Learning Group utilizes **deep learning**, a most advanced type of artificial intelligence for the high-throughput identification and characterization of various neurons. Their unique approach builds on advanced microscopic and electrophysiological techniques, and aims to **map the morphological and electric characteristics of neurons, as well as the processes of communication within this specific network of cells**.

The Biological Barriers Research Group is engaged in developing innovative solutions for **efficient drug delivery into the central nervous system (CNS) through the blood-brain barrier**. The current project focuses on a small peptide which interacts with the glycocalyx layer on the surface of cells, and promotes the transport of biomolecules or nanoparticles across the blood-brain barrier into the CNS. Thus, it offers a promising tool to design effective novel therapies for neurological disorders.

The Neurovascular Unit Research Group performs single-cell and metabolomics studies to reveal how the cells forming the blood-brain interface are involved in aging-related processes. The research project aims to give insight into the mechanisms of brain aging, and is expected to prove or disprove the hypothesis that removing aging cells may mitigate or delay age-related changes of brain microvessels.

SCIENTIFIC SERVICES AVAILABLE AT BRC

Besides supporting institutional research, laboratories of BRC with state-of-the-art instrumentation offer specific analytical tests for other research facilities from Hungary and abroad, as well as for pharmaceutical and biotechnology enterprises. Some of these scientific services are unique in Hungary.

METABOLOMICS

Changes in the levels of metabolites (small-molecule intermediates of metabolic processes) are key to the successful adaptation of living systems to environmental and genetic perturbations. These changes of metabolite levels are not predictable; therefore, the **Metabolomics Laboratory of BRC** offers the determination of metabolite levels' changes using high sensitivity analytical approaches (e.g. liquid chromatography coupled mass spectrometry).

We provide **nationally unique, untargeted metabolomics services** to our partners and customers. Using this method we are able to reveal metabolite level changes without predefining the metabolites of interest to be measured, and also get insight into the underlying metabolic activity. The potential applications of untargeted metabolomics analyses cover a wide range of areas; of these, it is an especially useful tool in the fields of systems biology, biotechnology and multiomics analyses.

As part of our metabolomics services, we provide a complete range of services related to experimental setup, sample preparation, measurement, data analysis, and detailed reports. Using our systems biology expertise, we can also provide metabolic network activity analysis and support biological conclusions.

Targeted metabolomics measurements are also available in our lab to expand our untargeted metabolomics service, and answer questions regarding defined subsets of metabolic networks. These analytical approaches provide the highest qualitative and quantitative reliability for metabolite determination. Among others, we have methods to cover metabolites related to energy production and use in the body (nucleotide phosphates), as well as amino acids, and TCA cycle intermediates.

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Instruments available at the Metabolomics Laboratory of BRC

PROTEOMICS

With state-of-the-art instrumentation, a plenitude of proteomics analyses is available in the **Laboratory of Proteomics Research**. These LC-MS/MS-based applications for protein analyses range from simple protein identification to the mapping of complex protein networks, and even *de novo* sequencing of yet unknown proteins is feasible. Depicting the different modifications of proteins leads to a better understanding of their molecular functions, regulatory mechanisms and interactions, while quantitative comparisons enable **proteomic profiling in different physiological states or during the progression of a disease**.

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FUNCTIONAL GENOMICS

The **Laboratory of Functional Genomics**, operating since 2000, offers the possibility of individual or systematic analysis of gene expression, quantitative analysis of nucleic acids (RNA, DNA, miRNA, blood-derived circulating cell-free cfRNA) and DNA methylation on several platforms. **The laboratory conducts research activities on a collaborative basis, and also operates as a service provider**. Our collaborations are highlighted by numerous significant Hungarian and foreign partners. **Our main developments** include amplification of nucleic acids from minute tissue samples or from a few cells only, single-cell RNA sequencing methods, digital nucleic acid detection, and bioinformatics analyses of gene expression.

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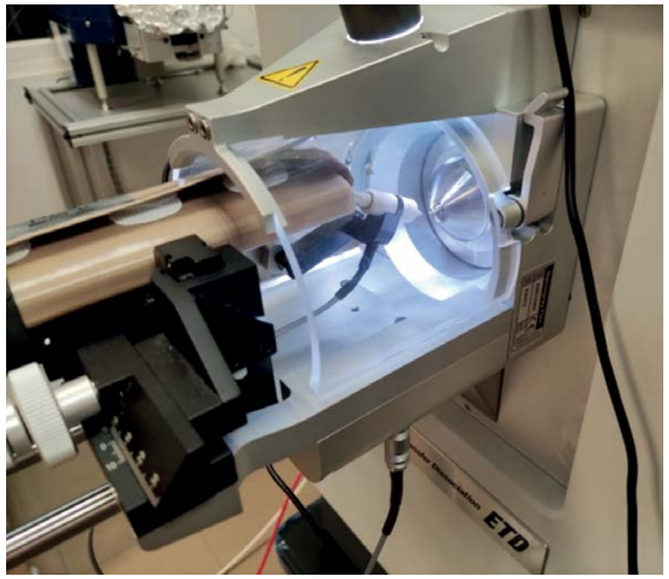
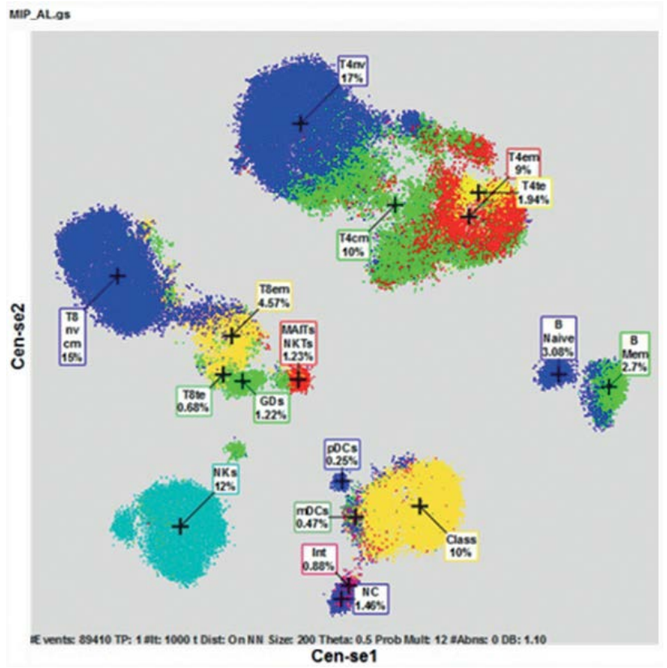
CYTOMETRY

The analytical tests executed at the **Cytometry Laboratory of BRC focus on disturbances of the activation and regulation of the immune system**. Molecular investigations (e.g. protein analyses) are performed to study human patient-derived blood or tissue samples at single-cell resolution. High resolution single-cell mass cytometry (CyTOF) is used to analyze the immunological characteristics of various immune cell types or cells from different cancerous samples (this process is called immunophenotyping). Comparative bioinformatics analyses of biological specimens (from



Ion source of an Orbitrap-type mass spectrometer



Immunophenotyping by single-cell mass cytometry (Cen-se map)

patients *vs.* healthy controls) are executed to reveal the differences in the expression patterns of proteins of interest at single-cell resolution. We have developed *in vitro/ex vivo* functional immune assays (i) to investigate immunomodulatory drug candidates, and (ii) to better understand the pathomechanisms and reveal signal transduction pathways behind the given pathologies. We have established wide national and international collaborations: numerous research groups and biotech companies lean on our expertise.

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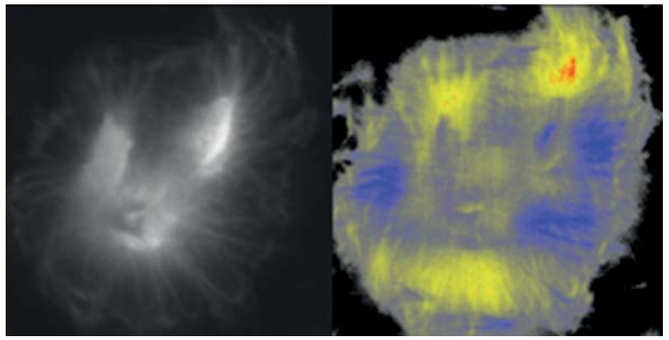
CONFOCAL FLUORESCENCE MICROSCOPY AND CELLULAR IMAGE ANALYSIS

The **Cellular Imaging Laboratory** offers confocal laser scanning microscopes, as well as stereo and epifluorescence microscopes for the researchers of BRC and other research institutes. Our **broad experience** serves the imaging tasks **in a wide variety of research areas**, including biology, medicine, geology and material science. We **provide image processing procedures/software and training** for manual and automatic processing of the acquired images. Adaptation to external needs covers hardware development and custom software development.



Self-assembling molecular complex visualized by differential polarization microscopy

Our laboratory is also equipped with **differential polarization microscopes for structural investigations of highly ordered molecular complexes**. Using differential polarization microscopy, a point-by-point mapping of the interaction between polarized light and matter can be executed to produce a 2D or 3D map of the key features of the anisotropic structure of the samples. Anisotropy most often manifests as birefringence (having two types of refractive indexes) or selective light absorption (photoselection); this is explained by the fact that elongated molecules in a biological sample respond to polarized light in a direction-dependent manner. Numerous examples demonstrate the existence of diverse forms of anisotropy in the structure of highly organized molecular systems of self-organizing living matter, biological samples and intelligent materials. The exploration and detailed characterization of these materials usually build on microscopy, hence the need to improve microscopic measurement techniques and further research in this area are essential for a better understanding of these biological phenomena.

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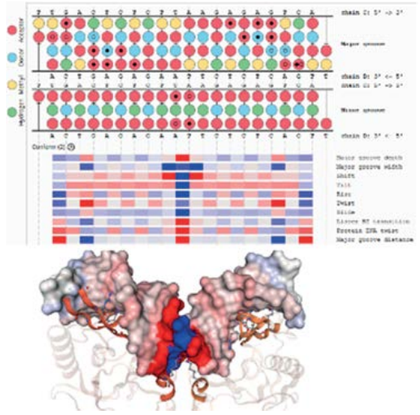
BIOINFORMATICS DATA ANALYSIS

The current paradigm of molecular biology is shifting towards the interpretation of data produced by high-throughput methods. The new data sources allow one to study system-wide properties in molecular terms. **We are developing novel, generalized knowledge representation schemes to study highly complex molecular systems of living cells**, like the regulatory network of gene expression. **The Bioinformatics Group has special expertise in large-scale bioinformatics data management systems** that have become an integrating force in systems biology, by providing common platforms and databases for different high-throughput experimental technologies. In recent years high throughput transcriptomics and the DNA structures responsible for gene expression regulation have become the major focus points of our scientific interest. To complement the conventional nucleotide-based DNA description scheme, we have **worked out novel DNA representation strategies** using a wide range of chemical, physical, and conformational DNA parameters which reflect the molecular structures responsible for sequence-specific DNA-protein interactions in a more direct and more intuitive manner. We have developed **DNA Readout Viewer** (DRV), a dedicated software system that displays DNA by using these new data representations, and exhibits the structural and functional features of DNA from a brand new point of view. This online visualization tool is freely available to the research community. As a result of recent scientific data boom, the **recognition of important hidden functional patterns and relationships in big data sets far exceeds the human cognitive capacity**, and not even traditional bioinformatics algorithms can perfectly cope with these problems. To address this issue, our current research aims to combine the above-mentioned novel DNA representation methods with different deep learning based data-mining approaches to decipher hidden DNA patterns in big data produced by high-throughput genomics investigations.



Molecular patterns observed in the recognition motif of I-PPOI DNA cleaving enzyme. The image is generated by the DNA Readout Viewer (DRV) software system developed by the Bioinformatics Group (available at https://drv.brc.hu/)

CONTACT:
HEGEDŰS, ZOLTÁN
(hegedus.zoltan@brc.hu)

CENTRAL ANIMAL HOUSE

The Animal House at BRC is responsible for the reproduction, housing and utilization of **commonly used laboratory strains of rats and mice**, as well as for the housing and maintenance of **transgenic mouse strains developed as disease models** by targeted gene modifications.

The animal house is operated by a staff of 5 qualified persons. In accordance with relevant regulations, it operates around the clock. Its hygienic classification is MD (minimal disease). Accordingly, the **hygienic state of the animal stock is tested twice a year**. The operating licence for the animal house authorised by the competent authorities covers housing and reproduction of experimental animals and their use in animal experiments, as well as supplier activities.

CONTACT
VERES, ERIKA
(veres.erika@brc.hu)

BRC LIBRARY

The constantly growing digital library stock at BRC covers the fields of biochemistry, biophysics, genetics and plant biology, with a special focus on molecular and cell biology. **Subscriptions for online journals and databases**, as well as the **textbooks and other scientific publications** available at the library **serve as valuable background material for researchers**. A digital catalogue of the complete set of the available books

is being prepared; to access the online catalogue please visit https://opac3.szbk.monguz.hu/search. The library's staff considerably facilitates scientists' work by e.g. recording publication activity and citations in the Database of Hungarian Scientific Works (MTMT) and extracting data from MTMT; uploading publications to the REAL Repository; providing scientometric data; managing the publication process, etc. A comfortable reading room and a computer room equipped with 10 terminals are also available at the library for the BRC staff.

CONTACT
PATKÓSNÉ HANESZ, ANDREA
(hanesz.andrea@brc.hu)

BRC DIGITAL PRESS

Free of charge for the BRC staff, the digital press of BRC provides numerous services that involve no material consumption or printing. These include digital photography with illumination or trans-illumination; digital photography of experimental laboratory equipment and experimental conditions; event and ID photography; scanning documents, slides, negatives, or retouching digital photos. **Other services available for BRC employees and external users for fee** include printing and photocopy of theses, photographs, posters, business cards; producing flyers; laminating, and preparing indoor project boards.

CONTACT
PATKÓSNÉ HANESZ, ANDREA
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INTERNATIONAL RELATIONS

Ever since its foundation, international collaborations supporting research, development and innovation (R&D&I) have been an integral part of the scientific endeavours of BRC. These relations guarantee that the eminent Hungarian research community is at the forefront of international life science research. International study visits and scholarships provide the possibility for young scientists to gain new perspectives and familiarize with the mentality of foreign research institutions.

NATIONAL LABORATORY OF BIOTECHNOLOGY

The system of National Laboratories is a programme launched by the National Research, Development and Innovation Office to support exploratory and experimental research. The main objective of the programme is the social, economic, and environmental utilization of research results. Within the frame of this programme, the **National Laboratory of Biotechnology**, operating at the Biological Research Centre in Szeged, aims to **exploit advanced biotechnology systems and achievements to develop unique and innovative approaches and therapeutic solutions in three main health-related fields**.

The first strategic objective of the National Laboratory of Biotechnology is to **develop effective strategies to fight against drug-resistant bacteria**. Partly explained by the genetic characteristics of bacteria, as well as by the extensive overuse of antibiotics even beyond the scope of human medicine, numerous new bacterium variants have emerged whose spreading cannot be inhibited by the available anti-bacterial agents. According to a World Health Organization (WHO) prediction, multi-drug resistant bacterial infections may cause more deaths than cancer by 2050, unless the current trends are reversed. We aim to develop novel multi-target antimicrobial agents that are effective against MRSA (methicillin-resistant *Staphylococcus aureus*), the multi-drug resistant bacterium responsible for numerous nosocomial (hospital-acquired) infections. Also, we aim to **develop an innovative biotechnological approach to produce therapeutic bacteriophages** against multi-drug resistant Gram-negative bacteria, in a rapid and controlled way.

The second strategic objective of the National Laboratory of Biotechnology is to **establish the first national research facility for the development of mRNA vaccines, with a focus on vaccine development against the African swine fever virus (ASFV)**. Vaccination is a widely used approach to combat serious infectious diseases. However, traditional vaccines may have several disadvantages. Those containing attenuated pathogens or purified proteins of pathogens often have reduced efficiency and may also carry safety risks. In contrast, **mRNA-based vaccination, which has been available for several years, is a revolutionary approach that opens new possibilities in this field**. RNA vaccine development is fast, cheap, and safe; thus, RNA vaccines may offer a solution to **deal with sudden outbreaks of pandemics or local epidemics. Our strategic aim is to introduce this revolutionary method of vaccine development in Hungary**. The African swine fever virus (ASFV) is a pathogen circulating in the wild boar population in our country, and is also a threat to the domestic pig population. We aim to produce an experimental mRNA-LNP vaccine against ASFV.

The third strategic objective of the National Laboratory of Biotechnology is to **identify the genetic causes of rare diseases and develop potential therapeutic solutions** by establishing authentic preclinical models and executing screens of libraries of active compounds of authorized medicines. Even though rare diseases collectively represent a serious healthcare challenge, they tend to be ignored by the profit-oriented pharmaceutical industry due to their low incidence per disease type. Via genetic engineering, authentic animal models of human diseases can be developed, which enable faster and cheaper screening for therapeutic agents. We aim to **create new animal models for an array of rare diseases to use them for the screening of potential therapeutic agents**. Our goal is to establish the first Hungarian research centre for screenings of repurposing libraries of authorized drug molecules. These screens may identify potential therapies for certain rare diseases that can be worth of further development by the pharmaceutical industry.

CONTACTS

DEVELOPMENT OF ANTIBIOTICS EFFECTIVE AGAINST MULTI-DRUG RESISTANT BACTERIA:
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DEVELOPMENT OF mRNA VACCINES:
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MODELLING RARE DISEASES, REPURPOSING DRUG SCREENS:
MIHÁLY, JÓZSEF
(mihaly.jozsef@brc.hu)

TALENT SUPPORT AT WORLD-CLASS LEVEL: THE NATIONAL ACADEMY OF SCIENTIST EDUCATION

The **Szeged Scientists Academy** was founded in the fall of 2013 by the Foundation for the Future of Biomedical Sciences in Szeged, on the initiative of Professor Péter Hegyi, PhD, organized with the leadership of Professor András Varró, PhD. The mission of the Academy was to attract young talents to Szeged, and to retain the most eminent young scientists in Hungary. This **internationally unique initiative** has grown into a vertical, multigenerational talent management programme, in which the Biological Research Centre, along with the University of Szeged, has played an important role from the very beginning. In September 2021, following the renaming of the Foundation to "National Biomedical Foundation", **this educational programme was extended** to include all Hungarian cities hosting universities for life sciences, namely Budapest, Debrecen and Pécs in addition to Szeged, and **has been run as a nationwide program renamed to National Academy of Scientist Education (NASE)** since then.

The primary task of NASE is to provide world-class training for future researchers in Hungary. University students committed to science are actively helped by NASE to broaden their scientific interests, starting as early as in their first year of university studies, and enable them to get involved in the highest-level scientific projects. **Students are trained in the country's best equipped laboratories located in six prominent scientific institutions of the four University towns, with professional supervision by "Szent-Györgyi mentors"**. In three Institutes of BRC, including the Institutes of Biophysics, Biochemistry and Genetics, 17 mentors and 7 junior mentors are actively engaged in supporting talented "Szent-Györgyi students". Some of these students have been awarded with the 'Student of the Year' Prize of this elite educational program. Efforts of the Szent-Györgyi mentors are backed up by an international mentoring group of nearly 60 outstanding scientists, including several Nobel laureates. **The short-term objective of the NASE program is still to support talented young students interested in biomedical research** to help them get engaged in scientific activities and provide an attractive model of the scientific career. **In the long run, the elite educational programme of NASE aims to retain talented young scientists in Hungary**.

Award-winners in 2022

SZENT-GYÖRGYI TALENT AWARD

In 2013, along with the foundation of the Szeged Scientists Academy, the Foundation for the Future of Biomedical Sciences in Szeged established the Szent-Györgyi Talent Award. According to the original concept, the award was to be granted to scientists working in Szeged, alike the Nobel laureate Albert Szent-Györgyi did, to **honour world-class prominent discoveries related to local research activities**.

Since the reorganizational establishment of the National Academy of Scientist Education (NASE) programme in 2021, the scope of the potential applicants for the Szent-Györgyi Talent Award has been extended to include scientists from Budapest, Debrecen and Pécs as well.

Awardees are jointly selected by Nobel laureates visiting the Academy's events, the scientific supervisors of the University Education Programme of NASE, and the members of the Board of Trustees of the National Biomedical Foundation. So far, nearly half of the award-winner scientists have been employees of BRC. The award is traditionally presented at the spring gala of the "Meetings of Nobel Laureates and Talented Students".

AWARD-WINNING SCIENTISTS

2013

PAPP, Balázs, PhD

Senior Research Fellow, Institute of Biochemistry, BRC

Awarded for the elucidation of the general characteristics of genetic interaction networks

2014

PÁL, Csaba, PhD

Senior Research Fellow, Institute of Biochemistry, BRC

Awarded for detailed mapping of antibiotic resistance of bacteria

2015

TAMÁS, Gábor, PhD

Professor, Department of Physiology, Anatomy and Neuroscience; Institute of Biology, Faculty of Natural Sciences and Informatics, University of Szeged

Awarded for the discovery of cells responsible for slow cortical inhibition and the description of its mechanism

PAPP, Balázs, PhD

PÁL, Csaba, PhD

HARACSKA, Lajos, PhD

HORVÁTH, Péter, PhD

NAGY, László, PhD

2016

HEGYI, PÉTER, PHD

Professor of the Faculties of Medicine of the University of Szeged and the University of Pécs

Awarded for clarifying the pathomechanism of acute alcoholic pancreatitis

2017

BERÉNYI, ANTAL, PHD

Assistant Professor, Institute of Physiology, Faculty of Medicine, University of Szeged

Awarded for elaborating the principles of electrotherapy of epileptic seizures

2018

HARACSKA, LAJOS, PHD

Scientific Advisor, Group Leader, Institute of Genetics, BRC

Awarded for research on carcinogenesis and description of new molecular entities affecting genome stability

2019

HORVÁTH, PÉTER, PHD

Director, Institute of Biochemistry, BRC

Awarded for elaborating the technique of intelligent image-based single-cell isolation

2020

NAGY, LÁSZLÓ, PHD

Senior Research Fellow, Institute of Biochemistry, BRC

Awarded for his outstanding research into revealing the evolutionary origin of hyphal multicellularity by comparative genomics

2021

MARTINEK, TAMÁS, PHD

Professor, Head of the Department of Medical Chemistry, University of Szeged

Awarded for his outstanding research related to protein delivery into cells using specific sequences to direct endocytosis

2022

DÉNES, ÁDÁM, PHD

Group leader, Laboratory of Neuroimmunology, Institute of Experimental Medicine (Budapest)

Awarded for his outstanding research related to compartment-specific modulation of neural and vascular responses by microglia

JUHÁSZ, GÁBOR, PHD

Senior Research Fellow, Institute of Genetics, BRC

Awarded for the elucidation of the canonic and non-canonic roles of autophagy genes

KOVÁCS, NORBERT, PHD

Associate Professor, Deputy Director of the Department of Neurology, University of Pécs

Awarded for his outstanding research related to improving the quality of life for patients with movement disorders, such as Parkinson's disease and dystonia

TÓTH, ATTILA, PHD

Professor, Department of Clinical Physiology, University of Debrecen

Awarded for his outstanding research to explore the gains and losses upon improving cardiac contractility

SOCIETAL ENGAGEMENT

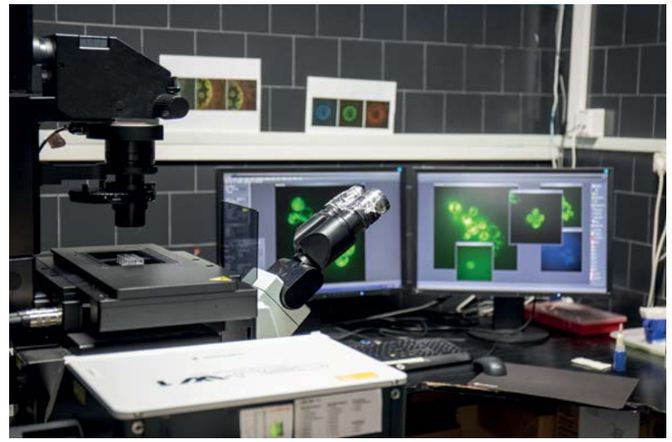
TALENT MANAGEMENT

Support for the education and training of future researchers has always been a priority at BRC. Within the framework of the **Biological Research Camp for High School Students**, organized with support from the Straub Heritage Foundation, talented high-school students come to Szeged from various locations in and outside Hungary, and get insight into the research performed in the laboratories of BRC. In collaboration with the University of Szeged, scientists **take an active role in coaching undergraduate students, as well as in mentoring PhD students**. We also **support the participation of young talents at conferences in Hungary and abroad**, so that they get the opportunity to present their research results to a wider audience.

Briefing for high school students at the Biological Research Camp

SCIENCE POPULARIZATION

Scientists at BRC are engaged in sharing their research experiences and providing an attractive model of the scientific career, as well as in popularizing natural sciences among elementary and high school students. Therefore, besides attending professional meetings and conferences on a regular basis, we often participate in scientific events organized for the general public. Upon the yearly international program series **"Researchers' Night"**and **"Brain Awareness Week"** BRC is open to visitors. On these occasions those interested can visit the laboratories, get acquainted with modern research equipment and methods, and talk to scientists informally about up-to-date science or the pros and cons of the scientific career. In addition, **BRC organizes regular visits for elementary, high school and university students**. We are regularly present at public events aimed at popularizing science, including those at the **Csopa Science Center in Budapest** and at the **"Science Laboratory" of Szent-Györgyi Albert Agora in Szeged**. BRC scientists are often interviewed in radio and television programmes, and write for popular science magazines.



COVID RESEARCH AT BRC

The scientific community all over the world responded to the Covid-19 pandemic with an unprecedented collaborative action. This unique and exemplary worldwide collaboration led to an extremely fast characterization of severe acute respiratory syndrome coronavirus 2 (SARS CoV-2), as well as the main factors affecting its infectivity, in no more than a few months' time. Within a year, effective vaccines were developed and approved to protect against serious and life-threatening disease. Due to the high variability (evolution) of the virus, many questions are still unanswered, including the scope of potential modifications of the virus in the long run, or the identification of patient characteristics applicable to predict the expected course of the disease. **Scientists at BRC actively participated in national and international Covid research from the very beginning of the pandemic. In addition to significant scientific achievements, they had an outstanding role in public education.**

GENOMIC ANALYSIS AND EVOLUTION STUDIES OF SARS-COV-2 VIRUS VARIANTS TRANSMITTED IN HUNGARY

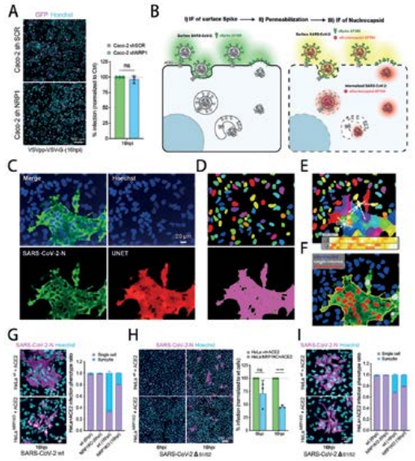
Even in short term (~1–2 weeks), the SARS-CoV-2 coronavirus spreading in the community accumulates mutations which can be identified by genome analyses of the variants isolated from infected patients. By tracing these mutations, the **temporal (evolutionary) and spatial patterns of these genetic variations provide important information on the spread of the epidemic**. For example, the number of separate introductions into a country, the geographical sources of individual centres of the outbreak, as well as the timing of the development of centres of infection can be assessed. Based on these data, the reproduction number of the virus can be calculated. Moreover, it provides valuable information on the transmission pathways of the epidemic as well. It should be emphasised that **evolutionary bioinformatics analyses of viral genomes provide unique information, independent of other epidemiological analyses**. This approach has been successfully utilized all over the world for the characterization of other epidemics, such as Ebola and influenza. **Via executing genomic analyses and evolutionary studies of SARS-CoV-2 coronavirus variants in Hungary, we aimed to reveal new aspects of the spread of the pandemic** in our country. The project was carried out **in collaboration with virologists from the University of Pécs**. Genetics mapping of about 200 SARS-CoV-2 variants circulating in Hungary were completed, indicating that the transmission patterns of the virus markedly differed in the first two waves of the pandemic. In the first wave extensive community spread was prevented by a timely national lockdown, whereas the second wave first remained unnoticed: the SARS-CoV-2 variant dominating this stage was introduced into the country early, with prolonged cryptic community transmission for several months before a soar of detected cases.

DISCOVERING THE KEY DETERMINANTS OF THE INFECTIVITY OF SARS-COV-2

An international research group involving scientists from the Institute of Biochemistry of BRC, led by researchers from the University of Bristol, have made a **breakthrough discovery regarding the infectivity of SARS-CoV-2 coronavirus**. Their findings **explain why the virus could become so highly infectious**, and why it spread so fast in the human body. In an original article published in the prestigious journal *Science* they describe the newly revealed role of a specific mechanism: the so-called neuropilin-1 (NRP1) receptor, located on the surface of host cells, is essential for the SARS-CoV-2 virus to get attached to and enter into the cell. The significance of the characteristic "spike protein" of SARS-CoV-2 had been recognized soon after the outbreak, while the key role of its specific subunit (motif) was revealed later, when scientists discovered that this motif interacts with the neuropilin-1 receptor to promote the infection of host cells. Using cell cultures, this collaborative international research work demonstrated that the interaction between the spike protein of SARS-CoV-2 and NRP1 host cell receptors are essential for viral cell entry, and drugs that selectively inhibit this interaction can reduce the infectivity of the virus. *Péter Horváth* and *Réka Hollandi* from the Institute of Biochemistry of BRC carried out the **detection of infected cell nuclei using NulceAIzer, a deep learning (artificial intelligence, AI) based algorithm the Horváth group had developed**. Detection is based on the different appearance (phenotype) of infected cells, as these have more than one nuclei in contrast to non-infected, healthy cells which contain a single nucleus. Besides detecting these cells, their AI-based method also quantified the burden of infection. These findings are significant for developing more efficient vaccines and new antiviral therapies against SARS-CoV-2.

AI-BASED COVID-19 SEROLOGICAL TEST

A worldwide unique, new serological test utilizing a combination of microscopy and artificial intelligence (AI) algorithms for the detection of immunity against SARS-CoV-2 coronavirus infection has been developed by researchers from BRC. It is based on detecting the antibodies produced by the immune system in response to the SARS-CoV-2 infection or vaccination. These antibodies remain in the circulation and are detectable from blood for several months, and provide an accurate feedback on the Covid-specific immune status of the individual tested. **The blood sample is mixed with cells modified to express viral proteins, which interact with the antibodies present in the sample, evoking a fluorescent signal**. Using a high-sensitivity, automated, high-throughput microscope, images of the sample are taken, and the presence or absence of the antibodies against SARS-CoV-2 is assessed for all individual cells using an AI-based method developed in our laboratory. The unique serological test to detect SARS-CoV-2-specific immunity is a product of joint development involving the Biological Research Centre, Szeged, the University of Helsinki and Single-Cell Technologies Ltd.



Detecting SARS-CoV-2 infected and non-infected control cell nuclei using NulceAIzer, a deep learning (artificial intelligence) based algorithm developed by researchers from BRC

'KOVIDŐK' FOR PUBLIC EDUCATION ON COVID 19-RELATED ISSUES

During the pandemic, Covid-19 was a hot topic in the general public, sadly exposed to the destructive effects of fake news and misinformation. In addition to valid scientific news, a great deal of fake news were circulating and disseminated from the very beginning of the outbreak. **The 'KOVIDők' project for public education was launched with the mission of disseminating reliable information to block the spread of fake news** often causing panic. **By interviewing independent specialists** (researchers, medical professionals) about the actual hot topics related to the pandemic, and **disseminating short articles and infographics** for the public **we aimed to improve health literacy**. We believe that as scientists we can (could) have a role in raising public awareness by providing credible and reliable information, and could promote the joint efforts required to stop the pandemic.

The KOVIDők Team was headed by two scientists of BRC (Péter Horváth, PhD and Bálint Kintses, PhD), supported by a volunteer staff of five biologists, a journalist, an IT specialist, a graphic designer and a social media specialist. **Hot topics were reviewed weekly in Facebook posts, roundtable discussions, infographics, interviews and short articles**. The Facebook page of KOVIDők had more than 50,000 followers, and **our posts directly reached more than 2.5 million people**. In addition, major television broadcasts of several channels regularly reported on our activities, and many online news portals also adopted our publications on a regular basis.

INSIDERS' VIEW – HOW DO SCIENTISTS SEE THEIR HOME INSTITUTION?

How do scientists working at the Biological Research Centre, Szeged (BRC) think about their home institution? What are its main values? How do they judge its atmosphere and the opportunities it offers? Is the sense of belonging to BRC a valued priority? What makes a workplace friendly and attractive? What are researchers inspired by? Scientists working at BRC share their opinion, based on their experiences of years/decades spent in the Institution.

Why do you like working at BRC?

"The Biological Research Centre has provided a supporting and inspiring environment for me ever since I started working here as a young scientist. The life and performance of many of my colleagues serve as a model for me and many others. A workplace with an outstanding professional standard, coupled with great human relations and a positive atmosphere is of particular value."

DELI, Mária
Member of the Institute of Biophysics since 1990

DELI, Mária

WILHELM, Imola

"In my career, I have experienced all my successes and failures here. I have learned that research is full of joy and challenges, and enthusiasm is accompanied by the constant need to restart. Last but not least, I love being a member of BRC because it always provides me with good reasons and great examples for further improvement."

WILHELM, Imola
Member of the Institute of Biophysics since 2003

"The atmosphere of BRC is youthful and friendly, and professionally inspiring. The environment is pleasant, and communication with the colleagues is informal. Proper conditions to support that I enjoy coming to work in the mornings, and feel motivated to concentrate on my research."

PORKOLÁB, Gergő
Member of the Institute of Biophysics since 2016

"Even as an undergraduate, I greatly enjoyed coming to work to BRC, because my ideas about the experiments were always listened to and considered, making me feel I was part of the team."

GÖRÖG, Péter
Member of the Institute of Genetics since 2017

"From my first day as a member of BRC, I have been regarded as a peer colleague, a full member of a team, part of a cohesive community. As we all know the others' research topics and challenges, we always know who to ask for help upon difficulties, not only in professional, but also in personal issues."

DUKIC, Barbara
Member of the Institute of Biochemistry since 2015

"I can always find some colleagues who are interested in the issues I am dealing with, and happy to join me in a discussion or even in an actual cooperation. Therefore, I never feel I am alone or isolated in my research area."

HONTI, Viktor
Member of the Institute of Genetics since 1996

"I love the inspiring environment of BRC. Seminars offer the opportunity to learn about others' research work, including not only the closest colleagues, but also foreign guest researchers. These discussions are excellent opportunities to share our thoughts on the latest scientific findings and to exchange experiences and ideas."

BENKŐ, Péter
Member of the Institute of Plant Biology since 2017

What are the main values of BRC in scientists' view?

"For me, the most important local values are excellent research groups, state-of-the-art laboratory instrumentation, value-oriented attitude, open-mindedness, accompanied by a supportive atmosphere, a great sense of humour, and the lack of a rigid hierarchy."

DELI, Mária
Member of the Institute of Biophysics since 1990

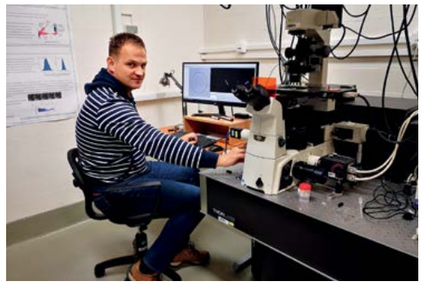
"I think that scientific and cultural diversity, as well as the support for young researchers and good ideas, irrespective of hierarchy, are unique values of BRC."

PORKOLÁB, Gergő
Member of the Institute of Biophysics since 2016

"For me, the main merit of BRC is the harmony of being successful in a highly competitive area, while surrounding us with a friendly and supportive atmosphere. The Institution has the »critical mass« for successful research, where scientists and non-scientists all know and help each other."

WILHELM, Imola
Member of the Institute of Biophysics since 2003

BENKŐ, Péter



VIZSNYICZAI, Gaszton

"I think that cutting-edge research in various fields of science, along with mentoring PhD students and providing practical education for the next generation of scientists are significant values of BRC."

VIZSNYICZAI, Gaszton
Member of the Institute of Biophysics since 2008

"Although BRC is regarded as a large institution on a national scale, everyday life for us is dominated by a kind of homely atmosphere, informality and cohesive attitude."

MICZÁN, Vivien
Member of the Institute of Biochemistry since 2021

"Respect of research and honour of the researchers' performance; an infrastructure enabling internationally competitive scientific activities; a stimulating environment and a democratic atmosphere all make valuable circumstances for an efficient personal development."

KISS, Antal
Member of the Institute of Biochemistry since 1975

"BRC offers the possibility for those with motivation and persistence to perform high-level research. The scientific attitude inherent to BRC for generations makes the Institution unique among national research facilities."

CSORDÁS, Gábor
Member of the Institute of Genetics since 2007

"Humanity and treating scientists as individuals are the main values of BRC for me. Here, the entire career of a scientist may expand in an Institute, within a supportive scientific community. Another important aspect is that BRC insists on its original mission of basic research, serving as a warranty for high-quality science and preserving values in an era dominated by constant changes."

HONTI, Viktor
Member of the Institute of Genetics since 1996

"In BRC all conditions for high-quality research are guaranteed, including cutting-edge infrastructure, personnel requirements and collaborations with the local university. International reputation and acknowledgement, open-mindedness and strong traditions are unique assets. The main measures of performance are individual achievements and creative ideas. Hierarchy is of marginal importance."

MARÓTI, Gergely
Member of BRC since 1999

"I have visited and worked at quite a few academic organizations in Europe, and have not seen many that offer better opportunities than BRC to truly focus on trying your scientific ideas. As a researcher, even at a junior level, you have considerable freedom to pursue those questions that most interest you. And what can be more rewarding and engaging for an experimental scientist than the joy of curiosity-driven experiments?"

LAMBREV, Petar
Member of the Institute of Plant Biology since 2010

KISS, Antal

MARÓTI, Gergely

What do the "BRC brand" and belonging to the Institution mean for the scientists working here?

"It means feeling at home. BRC has been my only workplace, it is like my home. I am now an emeritus scientist, but I am still glad to come to work each morning, just like I enjoyed it as a beginner. Through all these decades of fluctuating circumstances, BRC has remained a stable 'resort' as an internationally acknowledged institution and an attractive workplace. I am proud of having played an active role in the first 50 years of its existence."

KISS, Antal
Member of BRC since 1975

"BRC has a **b**rightly liberal and **r**ather inclusive atmosphere, and **c**oncentrates on research rather than mannerism. For young scientists it is sort of a »West nest« you love to belong to."

PORKOLÁB, Gergő
Member of the Institute of Biophysics since 2016

"In BRC »rank« is defined by knowledge, experience and professional achievements. I value this concept, and try to imprint it on the minds of my young colleagues in my group. In addition, joint activities like excursions, parties or Santa Claus events are special occasions to strengthen human relations."

DELI, Mária
Member of the Institute of Biophysics since 1990

"I am proud to work in one of the leading institutions of Hungarian life science research, internationally acknowledged as a prominent research facility."

VIZSNYICZAI, Gaszton
Member of the Institute of Biophysics since 2008

"For me the »BRC brand« means relevance. We are engaged in finding solutions for unmet needs and relevant biological issues as parts of a supportive and enthusiastic community, using state-of-the-art methods and equipment."

GÖRÖG, Péter
Member of the Institute of Genetics since 2017

"Each research group has its own expertise and personality. This diversity is a unique strength of BRC."

CSORDÁS, Gábor
Member of the Institute of Genetics since 2007

"I was born in Szeged, and even as a child I was familiar with the large building of BRC. I knew that clever men and women did scientific research there. At that time it was like science fiction for me. As an adult and a researcher, I feel happy and proud to work in this Institution which has long traditions and a long history of world-famous projects and achievements."

SIPKA, Gábor
Member of the Institute of Plant Biology since 2015

"For me, BRC gives the pleasure of belonging to an excellent research institution characterized by stimulating competition, mutual respect and high-standard science as the core values."

TÓTH, Szilvia Zita
Member of the Institute of Plant Biology since 2006

Are there any special opportunities at BRC?

"In Hungary, the intellectual and laboratory instrumental capacity of BRC are unique, allowing for excellent collaborations, often forming within the Institution."

PORKOLÁB, Gergő
Member of the Institute of Biophysics since 2016

In our Institute, trained scientists from many different areas, including physicists, biologists, chemists and medical professionals work together on various projects, enabling a real interdisciplinary approach and highly successful collaborations."

DELI, Mária
Member of the Institute of Biophysics since 1990

"In cooperation with the University of Szeged, BRC concentrates a significant research infrastructure and intellectual capital in the middle of the city. However, in contrast to the university staff, student education is not an obligation but a potential for us."

WILHELM, Imola
Member of the Institute of Biophysics since 2003

CSORDÁS, Gábor

TÓTH, Szilvia Zita

"Besides having the opportunity to learn from the most experienced scientists at BRC as a student, we are also offered the chance to attend national and international conferences, which is not only encouraged but also supported by the Institution."

DUKIC, Barbara
Member of the Institute of Biochemistry since 2015

"In BRC, the potential for collaborations support the efficiency and success of research, and also provide a fertile environment for professional development, including mastering in up-to-date research topics and methods. Collective reflexion allows the most complex approach for scientific issues which are thus examined from many perspectives."

HONTI, Viktor
Member of the Institute of Genetics since 1996

"In BRC the scope of possibilities are widescale. It is individual ambition and talent that drives how you make use of them."

MARÓTI, Gergely
Member of BRC since 1999

EDUCATION

STUDENTS' SCIENCE CLUB

In close collaboration with the University of Szeged, BRC offers the **opportunity for university students to join research groups** in order to work on their BSc or MSc diploma work. The majority of these undergraduate students are molecular biologists, but we also have students with other backgrounds, such as chemistry, physics or medicine. The Students' Science Club is the **main source of the next generations of scientists for BRC**: the majority of our PhD students are selected from those who did student research in one of our laboratories.

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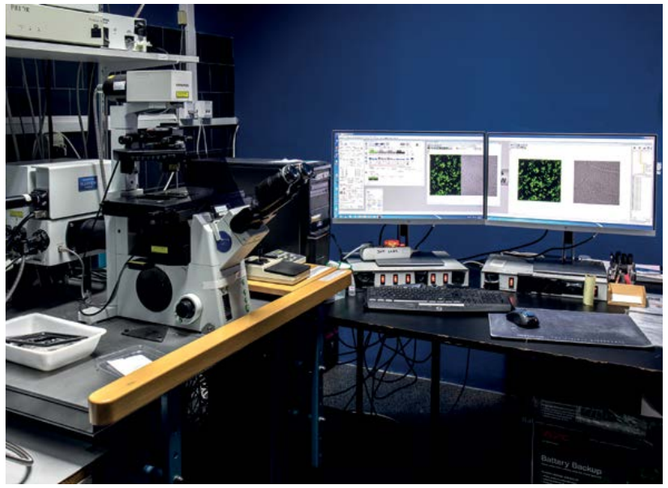
DOCTORAL SCHOOL

In collaboration with the doctoral schools of the University of Szeged, the Biological Research Centre offers **opportunities for PhD studies for fellows with Master's degree in the fields of biophysics, biochemistry, genetics and plant biology**. PhD students are mentored by the scientists of BRC. On average, BRC hosts about 70 postgraduate PhD students per year, mainly biologists, chemists, physicists and medical professionals, who work under the leadership of senior researchers of the accommodating research groups. Talented and motivated students may obtain their PhD degree within 4–5 years in average. Many of the brightest and most ambitious postgraduates can continue their research career at BRC.



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