# *Interdiszciplinary Medical Sciences (D93)*
## The Leader of the Doctoral School: Dr. Sümegi Balázs

## A-129/1993 Molecular and cellular biochemistry Program leader: Dr. Sümegi, Balázs

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| **Dr. Berente, Zoltán**<br>zoltan.berente@aok.pte.hu | Department of Biochemistry and Medical Chemistry | **Magnetic resonance imaging (MRI) and spectroscopic (MRS) study of various disease models in vitro, in situ and on small animals in vivo** |
| Nuclear magnetic resonance, due to its inherently advantageous properties, is especially suitable for noninvasive and nondestructive study of the living material (cells, tissues, intact living creatures). The method provides morphological, cellular (e.g. diffusion and perfusion) and molecular (e.g. metabolite concentrations) information practically simultaneously and in a spatially resolved manner. A further advantage of the method is that using non-radioactive isotope labelling it provides the localisation of the label not only among but also within the metabolites (i.e. which carbon atom(s) of a certain metabolite become(s) labelled). The planned studies are aimed at identifying in vivo detectable and quantifiable markers that indicate the extent and progression of the damages present in disease models. A further objective is monitoring these markers during experimental therapies (e.g. application of drug candidates) in order to characterise the efficacy of the therapy. The applicant will join the work of the MR lab in the Szentágothai Research Center of University of Pécs. The lab is already equipped with a Bruker Avance III 500 NMR spectrometer (11.7 T magnet) and during the year 2015 a 4.7 T small animal MRI instrument will be installed. | | |

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| **Dr. Gallyas, Ferenc**<br>ferenc.gallyas@aok.pte.hu | Department of Biochemistry and Medical Chemistry | **Identifying new molecular targets in oxidative stress** |
| Oxidative stress is considered as a major pathogenic factor in various diseases. Under pathophysiological conditions macrophages, monocytes and neutrophil granulocytes produce high amounts of reactive oxygen species and various cytokines that can induce cell and tissue damage. These processes occur locally in ischemia-reperfusion related maladies such as cardio- and cerebrovascular diseases, as well as globally in multi organ failure in septic shock. The initiative damaging agents, the reactive oxygen and nitrogen species produced by various processes impair certain intracellular components such as nucleic acids, proteins and lipids. These damages can lead to necrotic or apoptotic cell death by activating specific intracellular signalling pathways. The aim of the PhD project is identifying novel signalling pathway elements or other drug targets that can be used for developing new therapeutic strategies in oxidative stress related diseases. | | |

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| **Dr. Nagy, Péter**<br>peter.nagy@oncol.hu | Department of Biochemistry and Medical Chemistry | **Mechanistic biochemical investigations of Hydrogen sulfide signaling** |
| The medical importance of endogenously produced small signaling molecules is highlighted by the 1998 Nobel Prize in Medicine, which recognized the physiological mediatory role of nitric oxide (NO). The newest member of small signaling agents is hydrogen sulfide, which is generated in vivo during metabolic pathways of cysteine [1] . The field of H2S biology has exploded in the past decade [2], which (as a usual consequence of rapidly growing research areas) entails an increasing number of controversial observations in the literature. Our research group is dedicated to reconcile some of these controversies by studying the underlying molecular mechanisms of sulfide's biological actions [3, 4]. We are interested in the following three major pathways of sulfide | | |

signaling: 1) Orchestrating the functions of thiol proteins and protection against oxidative stress via sulfide-mediated persulfide formation. [5-8] 2) Interactions of sulfide with metalloproteins (coordination vs redox chemistry at the active sites). [7, 9] 3) Cross-talk between NO and sulfide signaling via chemical reactions between NO, sulfide, persulfides and nitroso-thiols [10, 11] The PhD candidate will undertake a rigorous biochemical investigation of one (or more) of the above pathways.

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4. Nagy, P., et al., Chemical aspects of hydrogen sulfide measurements in physiological samples. Biochimica et biophysica acta, 2014. 1840(2): p. 876-91.
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## B-130/1993 Investigating functional protein dynamics using biophysical methods — Program leader: Dr. Nyitrai, Miklós

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| **Dr. Bugyi Beáta**<br>beata.bugyi@aok.pte.hu | Department of Biophysics | **Investigations of protein-protein interactions in the organization of the sarcomeric thin filaments** |

During muscle development, de novo formed myosin and actin filaments assemble into the greatly organized sarcomeric structure critical for muscle function. Although sarcomerogenesis clearly involves the formation of novel actin filaments, it has so far been poorly understood how these filaments form. Two key steps of filament formation are nucleation and elongation. However, in muscle cells the essential actin nucleation and elongation factors, regulating actin filament formation, have not been clearly identified, and the mechanism that ensures sarcomeric thin filament assembly remained mysterious. Recently, we found that DAAM family formins, well known actin nucleation and elongation factors in nonmuscle cells, also play an essential role in sarcomerogenesis, whereas others identified the SALS protein as a key regulator of thin filament elongation. The major objective of our research is to investigate the molecular and cellular mechanisms of thin filament assembly during sarcomerogenesis by the detailed analysis of the functions of DAAM family formins and SALS. We aim to use the combination of genetic, cellular and in vitro assays (fluorescence spectroscopy, fluorescence microscopy, reconstituted biomimetic approach) to reveal the functional properties of these proteins, and to explore their molecular interactions with each other and with the known regulators of thin filament formation. We expect that the complex approach proposed will help us to gain deeper insights into the mechanism of myofibrillogenesis, especially into the mechanism of thin filament formation and the integration of the actin and myosin filament systems.

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| **Dr. Lőrinczy Dénes**<br>denes.lorinczy@aok.pte.hu | Department of Biophysics | **Thermodynamic (differential scanning calorimetry, DSC) investigation of the intermediate states of ATP hydrolysis cycle (in rabbit psoas muscle)** |

Glycerinated psoas muscle fiber is a good biochemical and mechanical model of the intact muscle. The ATP-hydrolysis cycle runs on ms time scale, so we need a very rapid technics to investigate it. We can make a long-living intermediate states with the help of different phosphate analogues with life time which

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| fits to the measuring time of other techniques (e.g.: EPR and DSC). This way we are able to investigate the molecular dynamic and thermal stability of these states for the better understanding of muscle function. |

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| **Dr. Lőrinczy Dénes**<br>denes.lorinczy@aok.pte.hu | Department of Biophysics | **Conformational changes of skeletal and cardiac actin/myosin under the effect of toxic agents (phalloidin and jasplaklinolide) and free radicals. A DSC approach** |
| Glycerinated psoas muscle fiber is a good biochemical and mechanical model of the intact muscle. The muscle model and the intermediate states of ATP-hydrolysis cycle depend strongly on the environmental effects. Some of these stabilise the structure (e.g.: toxins) while the free radicals influence the function too through the damage of the structure. UV irradiation of hydrogen peroxide produces free radicals and these will be used to monitor the structural and functional consequences of pathological hydrolysis cycle. | | |

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| **Dr. Lőrinczy Dénes**<br>denes.lorinczy@aok.pte.hu | Department of Biophysics | **DSC investigation of various cartilages, external knee-ligaments, reconstruction of shoulder/muscle and ligaments in human and animal samples** |
| Our aim is to clarify the molecular background of the damages in physiological function and in case of external loading or injury in the above mentioned samples. This way we could help to understand the molecular background of pathological processes, to develop and check new surgical techniques as well as the rehabilitation after the surgery (in cooperation with Clinic of Traumatology). | | |

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| **Dr. Lőrinczy Dénes**<br>denes.lorinczy@aok.pte.hu | Department of Biophysics | **Monitoring the consequences of different surgical procedures by DSC** |
| Our aim is to clarify the molecular background of the damages in physiological function and in case of external loading or injury in the different organs. This way we could help to understand the molecular background of pathological processes, to develop and check new surgical techniques as well as the rehabilitation after the surgery. To support an experimental surgery background (in cooperation with the Department of Surgical Research and Techniques). | | |

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| **Dr. Lőrinczy Dénes**<br>denes.lorinczy@aok.pte.hu | Department of Biophysics | **Measuring service in the development of probiotoc dairy products, food-physics research joined to these problems/PhD project direction** |
| The aim is to develop easy spreadable and youghurt type probiotic products to improve the misfunction of digestive system, to reduce the osteoporose, to sustain better Ca/P ratio (in cooperation with Dairy Research Milker Kft.). | | |

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| **Dr. Lukács, András**<br>andras.lukacs@aok.pte.hu | Department of Biophysics | **Functional dynamics of photoactive flavoproteins revealed by ultrafast spectroscopy** |
| Nature has many elegant ways for sensing the light, using photoactive proteins like rodhopsins, xanthophins, photototropins or flavoproteins having very distinct pathways to regulate the photoresponse. In the frame of this project we are investigating the molecular processes of blue light sensing in cryptochromes – blue light sensors involved in regulation of circadian rhythm as well as magnetoreception in brids – and BLUF domain proteins – transcriptional antirepressors in photosynthetic bacteria. As the primary steps of the photocycle of these proteins are very fast – ranging from femtoseconds up to hundreds of picoseconds – we are using ultrafast spectroscopy in order to elucidate the mechanism. | | |

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| **Dr. Nyitrai, Miklós**<br>miklos.nyitrai@aok.pte.hu | Department of Biophysics | **The investigation of protein function and conformation by using biophysical methods** |
| The actin cytoskeleton plays essential roles in many cellular functions. The appropriate time and space control of these processes is critical for most of the cell functions, and manifested by more than 60 families of actin-binding proteins. The scientific questions of the students joining our research group will be centred around the many - yet unknown - details of these regulatory mechanisms. One of the major components of this education will be the understanding of the known mechanisms and analysing the corresponding part of the literature. As part of the process the students are expected to attend national and international conferences and workshops. After defining the research questions we will apply biochemical and molecular biology methods to purify the chosen proteins. The investigations will be carried out by using various biophysical methods, including many assays in fluorescence spectroscopy (both steady-state and time dependent), fluorescence microscopy (conventional, confocal, fluorescence lifetime imaging), calorimetry and rapid kinetic methods. The concept will be to find and describe molecular mechanisms in in vitro experiments, and then correlate them to functions and interactions in living cells. Considering the nature of these research topics the projects are available and suggested for students with background in either medical or natural sciences. | | |

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| **Dr. Talián Csaba Gábor**<br>gabor.c.talian@aok.pte.hu | Department of Biophysics | **Functional investigation of tropomyosin isoforms** |
| The members of the actin-binding tropomyosin family display a high structural similarity. While their expression is strictly regulated in space and developmental state, several isoforms are always present in the same cell type, and little is known about their division of labour. Tropomyosins can influence the stability and dynamics of actin filaments; however, their actual biological significance may be the modification of association and function of other actin-binding proteins. The aim of the present research in our institute is to in vitro express tropomyosin isoforms in order to reveal their interactions with other actin-binding partners, like gelsolin, cofilin, twinfilin, caldesmon, myosins etc. The measurements will be carried out after fluorescent labelling by spectroscopy methods and light microscopy. We also intend to express fluorescent proteins even in living neurons. The Ph.D. student will have the opportunity to acquire substantial expertise in various methods from protein cloning through molecular biology techniques to the above mentioned measurement procedures. | | |

## B-131/1993 Intracellular signal transduction pathways Program leader: Dr. Szeberényi, József

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| **Dr. Pap, Marianna**<br>marianna.pap@aok.pte.hu | Department of Medical Biology | **Investigation of endoplasmic reticulum stress in different tumor cell lines** |
| The endoplasmic reticulum (ER) has an essential role in the synthesis, folding and processing of secretory proteins. The ER is armed with a quality control system to ensure that only properly folded proteins leave the ER lumen. Accumulation of the unfolded/misfolded proteins activates the unfolded protein response, which can lead to the apoptosis of the cell. ER stress has a role in the development of several diseases, including cancer. Its selective induction might be a promising target of the p53-negative tumors. We analyze the role and mechanism of ER stress and try to find drugs which can induce ER stress in different cancer cell lines. | | |

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| **Dr. Sétáló, György**<br>gyorgy.setalo.jr@aok.pte.hu | Department of Biology | **Studying the differentiation and apoptosis of rat pheochromocytoma (PC12) cells** |
| Rat pheochromocytoma (PC12) cells don't require the presence of nerve growth factor (NGF) for their survival. Upon treatment with the peptide, however, they differentiate into a sympathetic neuron-like phenotype. The main transducer of the underlying signals is the extracellular signal-regulated kinase cascade. In the complete absence of trophic support the cells die by apoptosis. Our goal is a better characterization of these signaling processes. Our experiments are carried out using immunoblots and confocal laser scanning fluorescence microscopy. | | |

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| **Dr. Sétáló, György**<br>gyorgy.setalo.jr@aok.pte.hu | Department of Biology | **Studying growth factor signaling in rat pheochromocytoma (PC12) cells** |
| The project aims at the better understanding of intracellular signaling by polypeptide growth factors in a rat pheochromocytoma (PC12) model system. These cells undergo neuronal differentiation in the presence of nerve- and fibroblast growth factor (NGF and FGF, respectively). At the same time they respond with increased proliferation to epidermal growth factor (EGF) treatment. We investigate various components of signaling cascades during the cellular response, with special attention to molecular chaperones as part of the regulatory mechanisms. Immunological techniques like Western blot, immunoprecipitation and immunocytochemistry are used in wild type and mutant cell variants. | | |

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| **Dr. Sétáló, György**<br>gyorgy.setalo.jr@aok.pte.hu | Department of Biology | **Studying the activation and intracellular localization of enzymes in differentiating rat pheochromocytoma (PC12) cells** |
| Nerve growth facror (NGF)-treated rat pheochromocytoma (PC12) cells stop dividing and, accompanied by process growth, differentiate into a sympathetic neuronal-like phenotype. In the background complex signaling events induce altered gene expression. Extracelllular signal-regulated kinases (ERK1/2) and Src proteins are key elements of this enzymatic regulation. We investigate the phosphorylation and intracellular distribution of these enzymes as a function treatments. Currently we are using NGF or the proteasome inhibitor MG-132 to elicit differentiation. | | |

## B-1/2013 Analytic techniques in biochemistry and molecular biology — Program leader: Dr. Gallyas, Ferenc

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| **Dr. Márk, László**<br>laszlo.mark@aok.pte.hu | Department of Biochemistry and Medical Chemistry | **Mass spectrometry-based biomarker discovery** |
| In this study, qualitative and quantitative analyses of pathological biomarkers will be carried out. The results from clinical samples and model animals help to understand the molecular pathomechanism of the disease. Additionally, the better understand of molecular networking give the possibility for faster diagnosis and for a novel therapeutic approach. | | |

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| **Dr. Márk, László**<br>laszlo.mark@aok.pte.hu | Department of Biochemistry and Medical Chemistry | **In-vitro and in-vivo imaging mass spectrometry** |
| Imaging mass spectrometry (IMS) is a new developed technique that enables the evaluation of molecular signals direct in situ from the tissue surface or thin sections. MALDI and LAESI IMS are label-free techniques with the ability to visualize the distribution of even hundreds of biomolecules in a single measurement, maintaining the morphological integrity of the intact tissue by avoiding homogenization | | |

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| **Dr. Márk, László**<br>laszlo.mark@aok.pte.hu | Department of Biochemistry and Medical Chemistry | **Clinical proteomics, lipidomics, metabolomics** |
| All pathological process based on a complex networking of numerous biomolecules. Proteins, lipids and their metabolites are of a vital importance in medical sciences. In this study, the molecular interactions and chemical modifications of the resulted biomolecules will be determined by high-resolution accurate mass MS techniques. | | |

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| **Dr. Márk, László**<br>laszlo.lark@aok.pte.hu | Department of Biochemistry and Medical Chemistry | **Medical Applications of Multimodal Imaging Investigations** |
| Matrix-assisted laser desorption ionization (MALDI) imaging mass spectrometry (IMS) is a new developed technique that enables the evaluation of molecular signals direct in situ from the tissue surface or thin sections. MALDI IMS is a label-free technique with the ability to visualize the distribution of even hundreds of biomolecules in a single measurement, maintaining the morphological integrity of the intact tissue by avoiding homogenization. | | |

## B-449/1999 Human Molecular Genetics Program leader: Dr. Melegh, Béla

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| **Dr. Melegh, Béla**<br>melegh.bela@pte.hu | Department of Human Genetics | **Human Molecular Genetics** |
| The PhD program combines two main complementary directions: investigations of „Rare Diseases", which includes mainly monogenic diseases and studying polygenic diseases affecting larger populations. The research activity involves collaboration works among universities, national and European partners. In both areas it is notable that the Department has a remarkable Biobank, with numerous samples from these diseases. Our Biobank is part of the European network (BBMRI), the collection of the rare disease Biobank contains over 10000 samples. Neuromuscular diseases is part of the laboratories original research field. Our Biobank enables research on diseases which affect larger populations, such as inflammatory bowel disease, stroke, autoimmune diseases, metabolic syndrome, polygenic variants of coronary disease. As a related area our research work is spread on the investigation of pharmacogenetically and pharmacogenomically important polymorphisms as part of personalized medicine. Part of this course is the research of enzymes and transporters, which take part in drug metabolism. OCTN2, which plays a role in carnitine transport is also part of the course, because other than resulting in systemic carnitine deficiency it can lead to several diseases. The study of the carnitine system as part of mitochondrial studies is a traditional field of research in our department and as such is part of the PhD program. | | |

## B-1/2013 Analytic techniques in biochemistry and molecular biology

## Program leader: Dr. Gallyas, Ferenc

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| **Dr. Bock-Marquette, Ildikó**<br>ildiko.bock-marquette@aok.pte.hu | Department of Biochemistry and Medical Chemistry | **New perspectives in discovering novel molecular mechanisms of cellular and organ regeneration, sport therapy and performance enhancement** |
| The lack of physical exercise, the lifestyle of our century, leads to significant increase of numerous cardiovascular and locomotor diseases worldwide. Prevention became a critical task of the scientific and medical society. It is obvious to all, regular training not only ensures health, but may also reverse pathological processes of disease by beneficially enhancing cellular and organ regeneration. Therefore, the primary aim of our current study is to screen and detect the influence of various sport activities on the human body at physiological, cellular and molecular levels. Our goal is to establish a collection of naturally existing secreted small molecules (peptides, micro RNAs, ect.,) and to investigate their effects on tissue regeneration and repair. | | |

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| **Dr. Bock-Marquette, Ildikó**<br>ildiko.bock-marquette@aok.pte.hu | Department of Biochemistry and Medical Chemistry | **Integrated approach identifying small molecules that promote tissue repair and regeneration** |
| Heart failure is a consequence of an injured or diseased heart undergoing pathological remodeling to match cardiac output with the metabolic needs of the body. 8 million people are confirmed with heart failure in Europe and the USA combined. With few exceptions the prognostic benefits of current treatments are limited, resulting in high rates of morbidity and mortality. Regulatory pathways involved in cardiac development may have utility in reprogramming cardiomycytes to aid in cardiac repair. As an alternative to stem cell therapy we hypothesize that small, secreted peptides or their derivatives together with other small molecules such as microRNAs are alternatives for tissue repair stimulation. These molecules are believed to modulate the activation of resident cardiac stem/progenitor cell populations. A systematic approach to understanding the signaling mechanisms actuated by such proteins will benefit the design of novel therapeutic agents to promote cardiac repair and regeneration in adults and children. | | |