3.4. Report on the research activity of Team 1.
Development of Diagnostic and Therapeutic Procedures

1. Focus of the team

Team 1 comprises five individual laboratories, all focusing on understanding the molecular and cellular bases of a variety of pathological states. They are engaged in cutting-edge basic research aimed at providing better understanding of the molecular mechanism of highly socio-economically challenging pathologies with considerable impact on population health. The focus is on a complex approach to the research of human diseases, starting with molecular aspects at the level of genetic regulation of selected pathologies, to biological, biochemical and proteomic studies that are relevant both to the genesis and progress of the pathologies, and on identification of relevant diagnostic biomarkers. Model organisms and systems are also used to uncover novel functions of genes, their products, and the regulatory aspects. An important output will be identification of novel and efficient therapeutic approaches.

The common denominator of all projects addressed by Team 1 is the pathological state of the cell. More precisely, it is uncovering the molecular mechanisms underlying this state by profiling selected genes, detection of changes in the localization and modification of relevant proteins, and identification of additional molecules that are involved in the initiation and progression of the pathological state. Further, focus is on the preparation of a rationale for prevention and/or treatment of these states and design of diagnostic methodologies for monitoring the various pathologies. This approach is comparable with that of the contemporary top bio-medical research institutions and is likely to deliver breakthrough results published in leading journals and resulting in commercially applicable intellectual property.

2. Research activity and characterization of the main scientific results

In the period of 2015-2019, the team published 131 papers in peer-reviewed journals, three chapters in scientific books, filed two patents, and obtained 13 applied results. The efforts of the team are primarily focused on high-quality basic research with potential application of the results in the diagnosis and treatment of diseases. The scientific profile and the main results of individual groups are presented below.

2.1. Laboratory of Reproductive Biology

Our laboratory has extensive knowledge of assessing male reproductive parameters as markers of fertility disorders. We have been studying the molecular mechanisms of reproduction and the nature of specific sperm proteins that play a role in sperm maturation, sperm-egg interaction and early embryo development. Our area of interest covers monitoring of sperm quality in patients with testicular cancer and diabetes mellitus and characterization of sperm antibodies in infertile couples. Many of these antibodies are used in Centres of Assisted Reproduction and have been commercialized. The key role of trans-generational epigenetic de-regulation of microRNA expression induced by pollutants in germ cell differentiation has been proven.

Recently, we have been interested in detailed characterization of the dynamic rearrangement of cytoskeletal proteins and their partner proteins (IZUMO1, CD46, CD9, CD81, CD151 and integrins) (Fig. 1a) involved in sperm-egg fusion (Fig. 1b) (Frolikova et al., 2016) (Frolikova et al., 2018) (Frolikova et al., 2019) (Jankovicova et al., 2016) (Jankovicova et al., 2019) (Jankovicova et al., 2020). In addition, the role of acrosin inhibitor expression and crucial ubiquitin proteasomal complex during sperm maturation has been addressed (Manaskova-Postlerova et al., 2016) (Zigo et al., 2019). Epigenetic aberrations (selected histone modifications and DNA methylation) in spermatozoa, testicular tissues (Fig. 1c) and early embryos after exposure to environmental pollutants have been studied (Brieno-Enriquez et al., 2015) (Vieweg et al., 2015) and new related projects are planned. All

the ongoing research is supported by four grants of the Czech Science Foundation (GACR) and by a prestigious international bilateral grant with the German Grant Foundation (GACR-DGF). The outcome of this research is being translated into new diagnostic tools for identification of sperm parameters and selection of high- and low-quality sperm to be used in Centres of Assisted Reproduction (Fig. 1d). This translational research is supported by grants of the Technological Agency of the Czech Republic and the Agency of the Ministry of Health. Two European and two Czech patents have been submitted and are currently under evaluation.

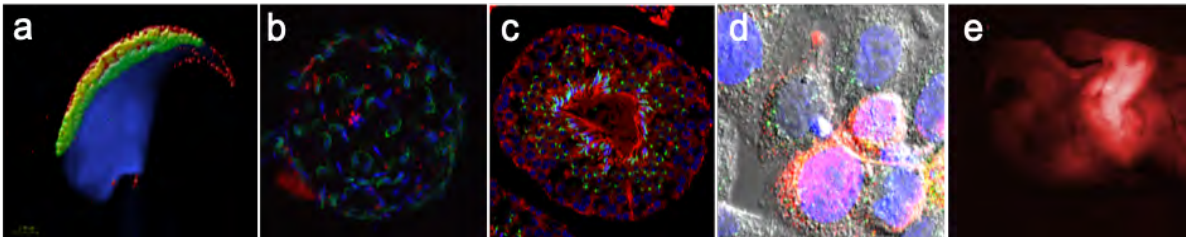


Fig. 1*. (a) Super-resolution microscopy (SIM) shows the localization of CD46 (green) on the inner and outer acrosomal membrane and β1-integrin (red) on the plasma and outer acrosomal membrane. (b) Super-resolution microscopy (STED) of a mouse oocyte shows the localization of proteins Izumo1 (green), Fcrl (red) and the nucleus (blue). (c) Testis: cross-section using transgenic mouse C57BL/6NAcr3-EGFP/Su9DsRed2, acrosome in developing spermatids and sperm (green), mitochondria (red), nuclei (blue). (d) CHO cells mimic the human egg model co-transfected with both JUNO (red) and fusion protein FcRL (green) with attached human sperm; nuclei (blue). (e) C57BL/6NSu9DsRed2 embryo: Red fluorescent protein expressed in mitochondria is visible under fluorescent light and confirmed by genotyping.*

We participate in productive collaboration based on the knowledge of detailed assessment of reproductive para-meters, monitoring of trans-generational epigenetic inheritance, characterization of epigenetic aberrations and microRNA deregulations, all tailored for specific areas of interest (medical conditions, lifestyle, environmental factors, etc.). In addition, we utilize, in collaboration with commercial subjects, our knowledge of hybridoma technology for production of specific high-affinity monoclonal antibodies (Merck, EXBIO), and 12 prototypes for the detection of relevant molecules have been developed. Moreover, we participate in valuable collaboration based on transgenic mouse lines, property of our laboratory, serving as an indispensable tool for in vivo experiments, specifically transgenic C57BL/6Acr3-EGFP mice expressing green protein (EGFP) in the sperm acrosome (Baert et al., 2019), and transgenic C57BL/6Su9DsRed2 mice expressing red fluorescent protein (RFP) in somatic cell mitochondria (Fig 1c,e) (Bajzikova et al., 2019) (Dong et al., 2017).

2.2. Laboratory of Molecular Therapy

Our laboratory has been focusing on several major projects plus additional side projects. The major projects, which have also provided high-level publications, include i) horizontal transfer of mitochondria; ii) design and testing of novel anti-cancer agents; and iii) the role of mitochondrial respiratory complex II in cancer. Our group published 56 papers in the last five years.

The discovery of horizontal transfer of mitochondria in vivo has been our most important discovery to date, since it is a finding of paradigm-shifting nature. In the initial paper, we describe the process, which is based on our result showing delayed tumour formation from cancer cells depleted of their mitochondrial DNA (mtDNA). These so called rho0 cells were found to form tumours only after acquisition of mtDNA from the host, as evidenced by the presence of mtDNA in these tumours with the host homoplasmic polymorphism (Tan et al., 2015). Further, we documented that mtDNA moves from stromal cells to cancer rho0 cells in vivo within whole mitochondria (Fig. 2) (Dong et al., 2017) and that the functional reasons for ‘import’ of mitochondria by cancer rho0 cells is due to recovery of their respiration; more specifically, we found that the reason is not related to ATP generation (which is provided by aerobic glycolysis) but is critically linked to de novo pyrimidine synthesis, since dihydroorotate dehydrogenase (DHODH), an enzyme critical for this pathway that is a component of the mitochondrial respiratory machinery, needs respiration for its catalytic activity (Bajzikova et al.,

2019). This discovery also indicates that DHODH may be a novel, broad-spectrum target for cancer therapy.

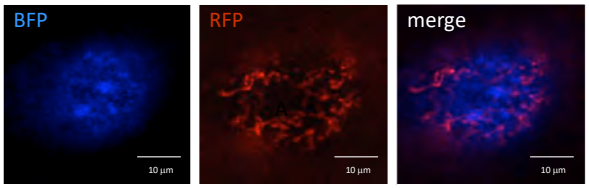


Fig. 2*. B16 rho0 cells with blue fluorescence protein nuclei were grafted in C17BL^{Su9DsRed2} mice with mitochondrial red fluorescent protein, and the tumour cells were recovered and sorted for red and blue fluorescence. The image shows a cancer cell with mitochondria of host origin.*

After mitochondrially targeted vitamin E succinate (Mito-VES) prepared some 10 year ago, we have synthetized several new anti-cancer agents targeted to mitochondria: mitochondria-targeted metformin (MitoMet) (Boukalova et al., 2016) and mitochondrially targeted tamoxifen (MitoTam) (Rohlenova et al., 2017). Both agents target mitochondrial respiratory complex I. We documented that MitoMet is efficient in killing pancreatic cancer cells expressing wild-type Smad-4, while cells with mutant Smad4 are resistant, and showed that MitoTam is efficient against a number of cancers, epitomized by the hard-to-treat Her2high and triple negative breast cancer. We filed a patent protecting MitoTam as a novel anti-cancer drug, which resulted in launching a Phase 1 clinical trial at the General University Hospital in Prague (EudraCT 2017-004441-25). At present, a Phase 1/1b clinical trial is in the final stages, with its end planned for June 30, 2020; until now, MitoTam has provided benefit (disease stabilization/partial remission) to 12 out of 26 patients tested in Phase 1b (long-term toxicity) (Fig. 3). We are currently planning Phase 2 with expected launch in 2021. Interestingly, we have also found that MitoTam selectively kills not only cancer cells, but also non-cancerous senescent cells via a mechanism involving the mitochondrial transporter ANT2 (Hubackova et al., 2018), and this is likely linked to replication stress (published in 2020: Hubackova S, Davidova E, Boukalova S, Kovarova J, Bajzikova M, Coelho A, Terp MG, Ditzel H, Rohlena J, Neuzil J (2020): Targeting of dihydroorotate dehydrogenase and checkpoint kinase 1 results in suppression of tumor growth via cell cycle arrest induced by replication stress. Cell Death Disease 11, 110). This discovery is a basis for our current studies of MitoTam re-purposing.

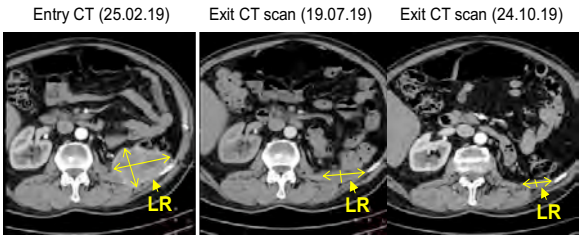


Fig. 3*. A clear cell renal carcinoma patient after left nephrectomy with relapse in the surgical bed was subjected to 3 rounds of 8-week regimen of Mito-Tam treatment, and the CT taken before the trial, after cycles 2 and 3. The red arrows point to the metastatic tumour that decreased over 40-fold.*

Based on our discovery of mitochondrial complex II (CII) as a new target for cancer therapy about 10 years ago, we have studied the biology and function of this complex in cancer (Bezawork-Geleta et al., 2017). We have shown that the catalytic SDHA subunit of CII, in spite of the general notion, does not need the assembly factor SDHAF2 for its flavinylation (Bezawork-Geleta et al., 2016), and we have found that under conditions of stress, CII is present in its partially assembled version, CII-low, comprising only SDHA and SDHAF2 and/or SDHAF4 (Bezawork-Geleta et al., 2018). We have recently characterized pheochromocytoma cells lacking the SDHB subunit of CII and proposed a possible therapeutic approach using ascorbate (published in 2020: Pang Y, Liu Y, Caisova V, Huynh TT, Taieb D, Vanova K, Ghayee HK, Neuzil J, Levine M, Yang C, Pacak K (2020): Targeting SDHB-mutated pheochromocytoma/paraganglioma (PCPG) with pharmacologic ascorbic acid. Clin Cancer Res (in press).

2.3. Laboratory of Gene Expression

Our Laboratory of Gene Expression is the leading Czech academic laboratory specialized in high-throughput gene expression profiling and single-cell analysis using RT-qPCR and RNA-Seq. In the period of 2015-2020, the team published more than 40 publications in peer-reviewed journals and one chapter in a scientific book. We have several research projects in the field of developmental biology

and neurobiology, and applied projects in cancer research and diagnosis. We are also involved in the development of methods and applications for nucleic acid analyses and standardization protocols for effective workflows.

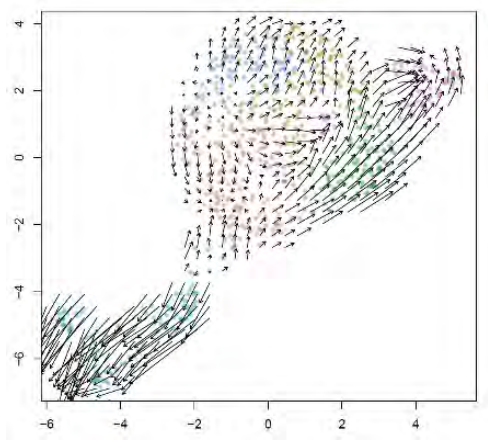


Fig. 4*. RNA velocity field describes differentiation of astrocytes after ischemic brain injury.*

Our group is very active in the areas of new method development and implementation. In the last five years, our laboratory developed a highly specific, sensitive and cost-effective system to quantify miRNA expression based on two-step RT-qPCR with SYBR-green detection chemistry called two-tailed RT-qPCR (Androvic et al., 2017). Using this approach, we have designed a two-tailed RT-qPCR panel for quality control, monitoring of technical performance, and optimization of microRNA profiling experiments from biofluid samples (Androvic et al., 2019). The technology has already been employed in several collaborative projects and currently is also offered as a service by the Gene-Core facility at the IBT. We are also involved in the process of standardization, having formulated aspects and recommendations for single-cell qPCR (Kubista et al., 2018), and we reviewed methods for single-cell collection and analysis (Valihrach et al., 2018) or for analysis of circulating miRNAs in cancer diagnostics and therapy (Valihrach et al., 2020). We have further compared performance of reverse transcriptases for single-cell studies (Zucha et al., 2019) or participated in multicentre evaluation of circulating plasma miRNA extraction technologies. In the field of single cell analysis, we have analysed factors that regulate the quality of single-cell suspension during dissociation.

In the field of neurobiology, our group focused on characterization of glial cells after brain and spinal cord injuries, during aging and in the progression of neurodegenerative diseases, especially of Alzheimer's disease and amyotrophic lateral sclerosis. We have studied the role of Wnt- and Shh-signalling pathways in prolifera-tion and differentiation of NG2 glial cells, the function of astrocyte in ischemia, the role of Trpv4 and Aqp4 proteins in cell volume regulation, or mechanisms of miRNA regulation in the nervous tissue after spinal cord injury. We have applied the most current approaches for gene expression analysis in the field, such as single-cell gene expression profiling and RNA-Seq (Fig. 4).

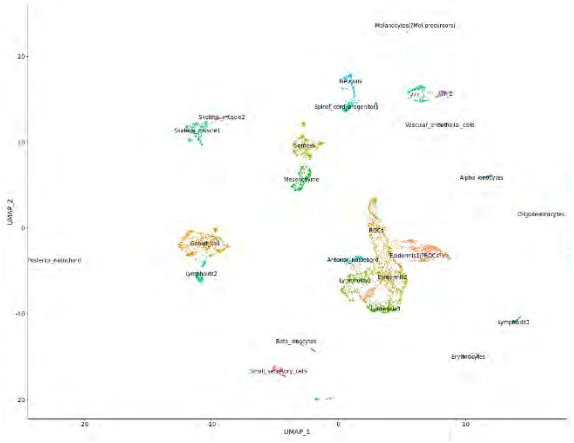


Fig. 5*. UAMP analysis representing single cell RNA seq of Xenopus wound healing.*

Xenopus laevis eggs and embryos are our prime models in our developmental biology projects. We study localization of maternal coding and non-coding RNAs and proteins using our own methods such as qPCR tomography and Tomo-Seq (Sindelka et al., 2018). Recently, we have utilized other animal models, such as sturgeon and zebra-fish for asymmetrical RNA localization studies. We have also studied regulation of embryonic wound healing and regeneration (Fig. 5), and we have determined a novel role for nitric oxide during healing (Abaffy et al., 2019) and revealed that nitric oxide is important for epidermis formation and function (Tomankova et al., 2017).

2.4. Laboratory of Molecular Pathogenetics

Our research programme is focused on transcriptional regulation during embryonic development, molecular mechanisms of developmental programming, and identification of the molecular causes of abnormal embryonic development and disease predispositions. We are particularly interested in HIF-

1, ISL1, SOX2, and NEUROD1 transcription factor networks and how their dysfunction affects embryonic development and can increase pre-dispositions of an individual to diseases such as diabetes, heart disease or hearing loss. We also analyse the combinatorial effects of the environment (e.g., diabetes) and genetic mutations. Using mouse models, cellular and single-cell and bulk transcriptome analyses, we analyse molecular mechanisms to identify targets for the development of preventive and diagnostic strategies.

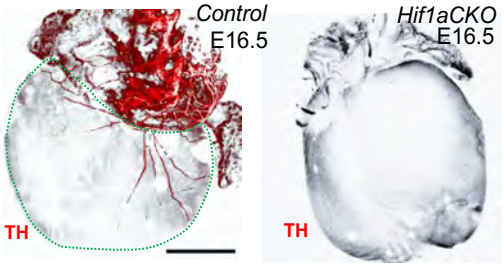


Fig. 6*. Abnormal development of sympathetic innervation in the Hif1aCKO embryonic heart, as shown by immuno-labelling of tyrosine hydroxylase (TH).*

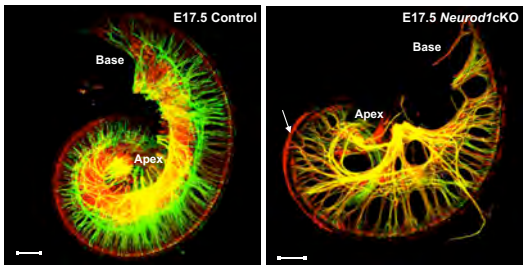


Fig. 7*. Deletion of Neurod1 results in aberrant formation of the spiral ganglion and innervation in the cochlea of Neurod1CKO compared to controls.*

We have continued our collaboration with Prof Semenza (Nobel Laureate in Physiology and Medicine, 2019; Johns Hopkins University School of Medicine, USA) on the role of HIF-1 pathways in cardiovascular pathologies and in combination with diabetic exposure. We showed that genetic deletion of HIF-1α results in increased cell death and decreased proliferation of neuronal progenitors of the sympathetic system and formation of cardiac sympathetic innervation (Fig. 6) (Bohuslavova et al., 2019). These findings suggest that dys-regulated HIF-1α expression may contribute to cardiac dysfunction and disease associated with defects in the cardiac sympathetic system, including sudden cardiac death and heart failure. Together with Prof Kolar's group (Institute of Physiology, CAS) and Prof Kubista's group (IBT, CAS), we showed that a global reduction in the Hif1a gene dosage increases predisposition of offspring exposed to maternal diabetes to cardiac dysfunction, and also underscore HIF-1 as a critical factor in the foetal programming of adult cardiovascular disease (Cerychova et al., 2018).

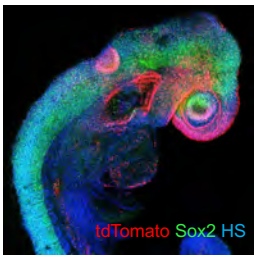


Fig. 8*. Expression pattern of Sox2 in E9.0 embryos.*

In the last five years, in collaboration with Prof Fritzsch (University of Iowa, USA) and Prof Syka's group (Institute of Experimental Medicine, CAS), we continued our research on the role of Sox2, Isl1 and Neurod1 transcription factors in the neuro-sensory development and function of the auditory system. Our data provide the first insights into the limits of physiology-mediated brainstem plasticity during the development of the auditory system (Fig. 7) (Macova et al., 2019); featured article in J Neurosci). We demonstrated that the absence of primary afferent topology in the inner ear leads to dysfunctional tonotopy of the auditory system. We showed that Isl1 mutation induces alteration in the efferent system and results in an early onset of age-related hearing loss (Chumak et al., 2016) and negatively affects GABA signalling in the brain with correlation to attention deficit hyperactivity disorder (Bohuslavova et al., 2017). We analysed the requirements for SOX2 during neurosensory development (Fig. 8) (Dvorakova et al., 2016). The inner ear provides a simpler model to study SOX2 involvement in neuronal specification, proliferation, and differentiation compared to the brain. We showed differential requirements of SOX2 for neuronal development in the Sox2 conditional deletion mutant, as all early forming vestibular neurons seem to develop normally; however, late-forming spiral ganglion neurons are not formed. Thus, these results address some fundamental questions of cell replacement therapy.

2.5. Laboratory of Tumour Resistance

The major research topics investigated in the lab are: i) elucidating the molecular mechanisms underlying cancer resistance, proliferation and recurrence; ii) developing novel approaches that target cancer cells based on mitochondrial targeting and interference with iron metabolism; and iii) deciphering the molecular mechanisms that govern appropriate systemic iron metabolism and the relation-ship between cancer and iron metabolism.

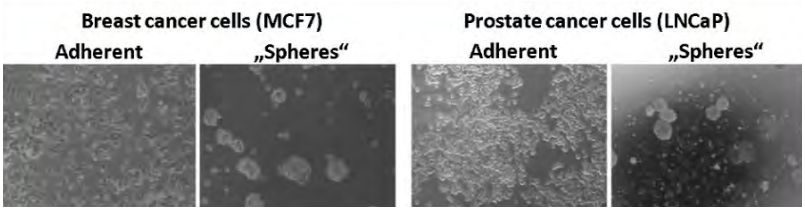


Fig. 9*. Appearance of cells growing in 3D as so called "spheres" that exhibit properties of tumour-initiating cells.*

Since there are many possible ways how cancer cells can develop resistance, we study several models of resistance. We cultivate and investigate the molecular profiles of tumour-initiating cells (TICs) that grow as three-dimensional (3D) "spheres" and more closely resemble real tumours (Fig. 9).

TICs show upregulation of the ABC transporters that confer resistance to commonly used anti-cancer drugs. We have published a pioneering work about iron metabolism in TICs (Rychtarcikova et al., 2017), where we describe the iron metabolism-related gene signature, document higher iron uptake, higher labile iron pool and accumulation of iron within mitochondria, a markedly higher ROS level and enhanced sensitivity to iron chelation in these cells.

We have also elucidated the molecular mechanisms that underlie tamoxifen resistance in breast cancer cells and we have found an increased level of mitochondrial superoxide and altered mitochondrial structure and function in these cells. In a recent report (Tomkova et al., 2019), we show that these cells exhibit extensive fragmentation of mitochondria and display markedly reduced levels of respiratory super-complexes assembled into supra-molecular structures called "respirasomes", which is associated with their lower enzymatic activity and decreased mitochondrial respiration. These findings thus suggest a link between tamoxifen resistance and decreased mitochondrial function. Importantly, we have shown that high expression of miR-301a-3P in oestrogen-dependent breast cancer cells results in inhibition of oestrogen signalling, thus participating in the transition to tamoxifen resistance (Lettlova et al., 2018).

One of the main topics of our group in collaboration with the Molecular Therapy Laboratory is mitochondrial targeting as effective anti-cancer therapy. In this regard, we have together identified a very strong anti-proliferative effect of MitoVES at doses that are non-apoptotic. The underlying mechanism is a considerable decrease in mtDNA transcription, particularly a decrease in the D-LOOP transcript both in vitro and in vivo (Truksa et al., 2015). The intracellular localization of MitoVES in mitochondria is shown in Fig. 10.

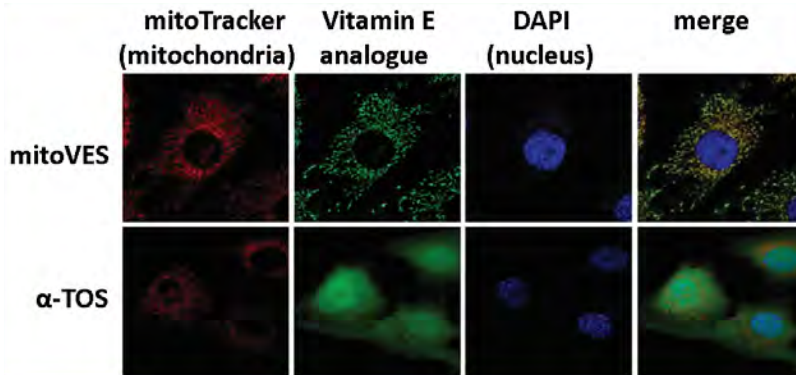


Fig. 9*. Intracellular localization of MitoVES and parental com-pound α-TOS, showing the presence of MitoVES in mitochondria.*

The last topic of the lab is systemic iron metabolism. We use the mouse model of iron deficiency iron refractory anemia (IRIDA) to study the iron metabolism, erythropoiesis and the regulation of erythroferrone (ERFE), transferrin receptor 2 and haemojuvelin in this model. We have been

successful in developing the assay to test the ERFE protein level in vivo and reported that its protein level is markedly upregulated in the mouse model of IRIDA despite its inability to respond to erythropoietin and mutated Tmprss6 gene (Frydlova et al., 2017).

3. Cooperation within international research area

Laboratory of Reproductive Biology intensively collaborates with several research groups from Europe (Germany, Slovakia, Spain, Belgium, UK), Australia, New Zealand, Asia (Japan, Taiwan) and USA (Missouri). Most of these collaborations have resulted in joint publications, some being in preparation. Cooperation with the laboratory of Prof Klaus Steger (Biomedical Research Centre, Giessen, Germany) is currently supported by a joint bilateral grant funded by the Czech Science Foundation and Deutsche Forschungsgemeinschaft. Collaboration with the laboratory of Reproductive Physiology, Centre of Biosciences, Slovak Academy of Sciences, Slovak Republic has been supported by bilateral grants between the Czech and Slovak Academies of Sciences that guarantee close scientific contacts between both laboratories. The cooperation between Taipei Medical University and IBT was approved in 2019 to support an exchange programme that will primarily be used by the group of Reproductive Biology.

Laboratory of Molecular Therapy has been collaborating with up to 30 various institutions, domestic and international. There are too many to list here. Suffice to say that their recent publication in Cell Metabolism (Bajzikova et al., 2019) lists 50 co-authors from 15 laboratories. Probably the most prominent collaboration is with Prof. Mike V. Berridge of the Malaghan Institute of Medical Research (Wellington, New Zealand), with whom Jiri Neuzil discovered the paradigm-shifting phenomenon of horizontal transfer of mitochondria in vivo.

Laboratory of Gene Expression cooperates with several laboratories across Europe (Elly Hol, Netherlands; Milos Pekny, Sweden; Henrik Ahlenius, Sweden; Anders Stahlberg, Sweden; Itamar Harel, Israel; Dolores Pérez-Sala Gozalo, Spain; Agnieszka Smieszek, Poland) and with the laboratory of Norman Dovichi, University of Notre Dame, USA.

Laboratory of Molecular Pathogenetics collaborates with different laboratories, both domestic and international, in particular with the following ones: Prof Agnes Görlach (German Heart Centre, Technical University Munich) researches the role of oxygen, reactive oxygen species and oxidative stress in the regulation of cell and organ function and specializes in the field of cardiac, circulatory and vascular disease. The collaboration incudes grant applications, exchange of PhD students, preparation of publications. Prof Bernd Fritzsch (University of Iowa, USA) - research programme focusing on the molecular biology of neurosensory systems in collaboration with, grant applications, preparation of publications, a PhD student visit. Prof Greg Semenza (Johns Hopkins University School of Medicine, Baltimore, USA) providing mutant mice, plasmids, antibodies, preparation of publications.

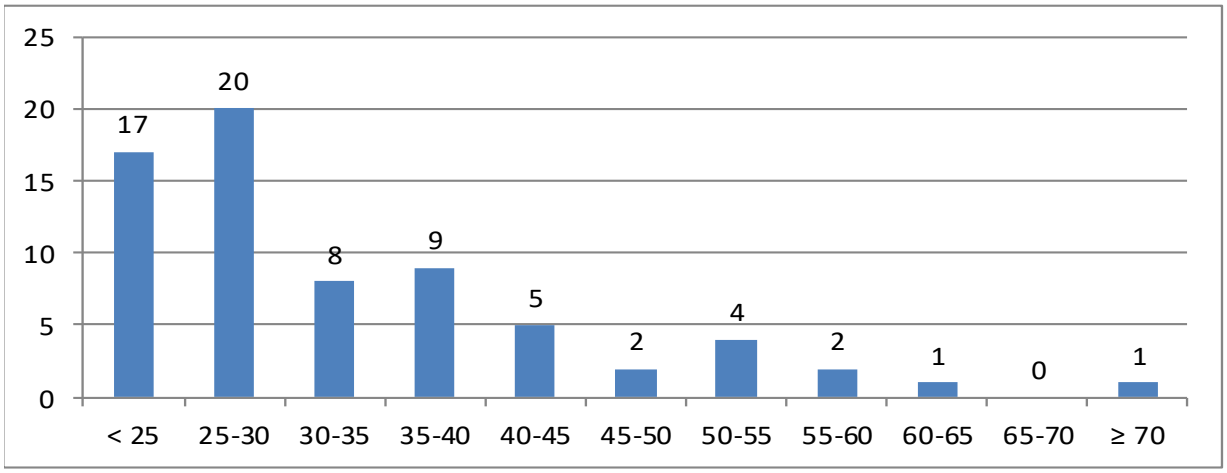
The Laboratory of Tumour Resistance cooperates with several international institutions and labs, one of them being the lab of Prof Tomas Ganz (David Geffen School of Medicine at UCLA, Los Angeles, USA), Prof Jiri Neuzil (Mitochondria, Apoptosis and Cancer Research Group, Griffith University, Southport, Qld, Australia), and recently we started collaboration with Prof Li Qiao (University of Michigan, USA)

4. HR policy of the team

HR policy of the Team is consistent with a modern approach to recruitment of young, talented researchers and their supervision. Our major drawcard, which allows us to inspire highly talented Czech and international students, is our excellence of research, great working international environment (we conduct our seminars, journal clubs and group meetings in English), access to world class facilities, etc., as well as providing highly competitive remuneration: for example, all our PhD students are provided scholarship plus salary corresponding to 0.5-0.8 position of research assistant. All supervisors within our Team are highly skilled and have ample experience from working abroad, as post-doctoral fellows or senior researchers (several laboratory heads of our Team have dual positions, one in the IBT, one abroad – for example in Sweden or Australia). An inherent part of our supervision is to motivate students to come up with their own ideas, apply for grants, and be actively involved in writing of research papers. This allows them to seek competitive post-doctoral positions after PhD graduation. Several of our former PhD students are now successful post-doctoral fellows in international institutions (in Sweden, United Kingdom, Belgium, etc.).

5. Age structure of the team

Age category	< 25	25-30	30-35	35-40	40-45	45-50	50-55	55-60	60-65	65-70	≥ 70
Number of members	17	20	8	9	5	2	4	2	1	0	1



6. Strengths and weaknesses

6.1. Strengths

Laboratories comprising our Team are involved in fundamental research within the discipline of biomedicine. One of the major strengths is that we cover a variety of research areas that we refer to as 'Healthy Journey Through Life'; in other words, we focus on the major pathological states that may affect human physiology from conception via embryogenesis, early years, and young adulthood, all the way to mature age. Thus, we cover research areas concerning fertility, embryogenesis, type 1 and type 2 diabetes mellitus, childhood as well as adult neoplastic diseases, senescence, heart disease, and neurological disorders affecting senior subjects. Importantly, we aspire to provide basic knowledge that can be translated to the clinic in order to enable adults in reproductive age to conceive new life.

All our groups have been engaged in world-class research, which is evidenced by publications in top journals, which include, for example, Cell Metab, Nat Commun, Proc Natl Acad Sci USA, Trends Biochem Sci, Clin Cancer Res, Nucl Acids Res, Mol Asp Med, Cell Death Differ, eLife, Clin Chem, Cell Death Dis, Antiox Redox Signal, J Neurosci, etc. Importantly, we have a number of manuscripts under revision or (to be) submitted in journals including Nat Rev Drug Discov, Nat Commun, Cell Metab, Nat Genet or Nature.

An important point that favours our research to be competitive at the world level is that our laboratories are headed by top scientists that are leaders in their respective areas of research. They are supported by highly qualified research fellows and PhD students. The 'human factor' is indisputably the major (and probably most important) asset of our Team.

Due to the high profile of our laboratory leaders, we have individually built a complex network of worldwide collaborations. These are spanning continents; thus, we collaborate with multiple laboratories in North America (Canada, USA), Europe, Asia (Singapore, Japan, South Korea, Taiwan, China) and Oceania (Australia, New Zealand), as evidenced by joint publications and, in some cases, international grants.

A strength of our Team is also ample funding that we are regularly acquiring, in particular from the National Competitive Grant schemes, including the Czech Science Foundation and the Czech Health Foundation. All of our groups are well funded, and the high level of financial support has been maintained over the time. Importantly, we have several joint grants with international collaborators. Also, the Laboratory of Gene Therapy has been successful in obtaining an EU grant in 2019. Another strong point is the equipment of our laboratories with high-end instruments for routine as well as highly specialized analyses. Also, we have ready access to world class core facilities within the BIOCEV Research Centre, including the Czech Centre for Phenogenomics (allowing us to prepare transgenic mice using cutting-edge methodology of gene editing), Centre for Imaging Methods (with a suite of cutting-edge microscopes), OMICS Proteomics Centre, as well as Gene Core Centre for Quantitative and Digital PCR.

The last strength worth highlighting is our capacity to translate our research to the clinic. This is best exemplified by the Laboratory of Molecular Therapy that has designed, synthesized and tested a novel anti-cancer agent, mitochondrially targeted tamoxifen, which is currently under Phase 1/1b clinical trial in the General University Hospital in Prague. Also, the Laboratory of Gene expression has been involved in the development of a new test confirming the presence of coronavirus (COVID 19) in the body, indicating that we very actively respond to current challenges.

6.2. Weaknesses

An important aspect that is essential for high-quality research is acquisition of sufficient funding. While we are well 'stocked' by funds at present, there is always the looming possibility of dwindling financial support for our research work in the future. Thus, while we need to focus our aspirations to obtain funding from the National Competitive Grant schemes, we have to diversify and also apply for more substantial funding, for example from the EU structures and other international providers.

As mentioned above, we are equipped with excellent, cutting-edge instruments, most of which were acquired when the BIOCEV Research Centre opened a few years ago. The potential problem is

associated with the fact that in several years, a number of these instruments will be obsolete and will have to be replaced with new models. We will therefore need funds to purchase the instruments, so that we not only maintain our high level of research, but further it towards world-class excellence.

The BIOCEV Research Centre is located just outside the territory of Prague, which makes it more difficult to recruit talented students for experimental work. Therefore, we need to liaise more with universities in the capital city (for example by giving lectures) to attract young talents to our laboratories and to be more 'visible' to potential international students.

7. Assessment of the activity plan of the team for the period 2015-2019

Our plan for the period of 2015-2019 was based on the strong points and high achievements of research of the previous period. The plan was to bring the strong points toward scientific excellence and to publish in top journals. We have undisputedly achieved this, as evidences by papers that we have published over the last five years. In total, we have published 113 papers in a variety of journals, from highly specialized journals to wide-scope journals with high impact factor. This is documented by several papers in Cell Metab (IF 22.4), Trends Biochem Sci (IF 16.9), Nat Commun (IF 12.1), Proc Natl Acad Sci USA (IF 9.6), Mol Asp Med (IF 8.31), or Cell Death Differ (IF 8.1) to name only a few representative journals in which we have published. We have also been involved in multiple international collaborations with prominent researchers all over the world, and have greatly enhanced the national and international reputation of the IBT. This is linked to presentation of the success of IBT in the media (see point 17), particularly due to successful translation of our research into clinical practice. This is epitomized by a clinical trial of our proprietary drug, mitochondrially targeted tamoxifen, which is being tested in patients with multiple types of cancer. The high level of our research within the last five years also gives promise to further improvement of excellence of our research, with several manuscripts submitted (some under revision) in journals such as Nat Rev Drug Discovery, Cell Metab, or Autophagy, and others will be sub-mitted to Nature, Cell Metabolism, Nat Genet, etc. This would not be possible without high level of institutional and, in particular, competitive funding, where we have more than 2-fold higher success rate compared to the national average. In conclusion, we have met all plans of our Team for the previous assessment period of 2015-2019.

8. Implementation of recommendations from the past evaluation

The International Committee that evaluated us for the period of 2010-2014, while highly appreciating our achievements, recommended that we focus the breadth of the topics that are covered by laboratories of our Team. While we understand this, we ought to state that the breadth of the topics that we cover (to which we refer to as the Healthy Journey Through Life) is, actually, arguably our great strength. In a nutshell, our constituent laboratories focus on pathological states that start from the conception of new life via embryogenesis, early years, and young as well as mature adulthood. By addressing specific pathologies (or states of dys-balanced physiology), we carry out high-level fundamental biomedical research in the broader discipline of cell and molecular biology pertinent to the specific pathological states and are trying to translate these results to the clinic, with considerable success. Therefore, we are adamant that this point raised by the Committee is our strength.

However, we complied with the recommendation at the level of individual laboratories, which have focused their research to be more streamlined toward the specific pathologies. This allows us to gain deeper insight into the molecular mechanism underlying the individual pathological states and to translate the particular discoveries into benefits for patients. Thus, we believe we took on board the recommendation in a plausible manner, and we thank the Committee for suggesting it to us.

9. Activity plan of the team for the period 2020-2024

The plans of future research of Scientific Team 1 stem from the projects listed above, focusing on their development and on aspiration for research excellence. This is highly feasible in our hands, due to the excellent recent profile of our laboratories epitomized by a number of publications in top

journals (see above for our representative publications) and ample funding from the National Competitive Grant system, in particular from the Czech Science Foundation and the Czech Health Research Foundation. Further, we have ready access to key core facilities.

9.1. Laboratory of Reproductive Biology

We plan to carry on further investigation in the field of sperm-egg membrane protein interaction (Frolikova et al.: in press 2020) and expand it to humans after successful application of ethical approval for human sperm-egg fusion experiments. In collaboration with Centres of Assisted Reproduction, Prof Moore (University of Sheffield, UK) and Prof Ikawa (University of Osaka, Japan), and other colleagues, we will target the predicted human specific egg plasma fusion receptor, and by a wide range of methods including transgenic cell lines mimicking the human egg, we intend to carry out excellent research that will be published in a high-impact journal. We will also focus on monitoring the fertility parameters of sperm and testicular tissue in patients with testicular cancer with respect to their therapy. Together with Prof Steger (University of Giessen, Germany), we have started studying the signal transduction pathway from sperm chromatin to the cytoskeleton applying state-of-art molecular techniques. Results from mice will be transferred to humans, investigating testicular biopsies and sperm from subfertile men. Data on protein-protein interactions involved in the nucleus-cytoplasm communication pathway will contribute to our understanding of chromatin integrity, chromatin-cytoskeleton network and sperm motility, leading to a pathophysiological situation in men. We plan to bring new important insights into the effect of natural and synthetic oestrogens on the process of protamination in testicular tissue, epigenetic profile in testicular cells and sperm, and to evaluate its heredity and effect on early embryonic development.

9.2. Laboratory of Molecular Therapy

We will further study the molecular mechanism of horizontal transfer of mitochondria and its functional consequences including its translational context. At present, we have a manuscript documenting movement of mitochondria along tubulin fibers, performed in collaboration with Dr Lansky (IBT, CAS), under revision in Nat Commun, plus a manuscript under revision in Cell Metab, where we show that platelets donate mitochondria to mesenchymal stem cells that promote wound healing in collaboration with a team from Universite Paris-Est). We will continue in our efforts to design, synthetize and test novel, mitochondria-targeted anti-cancer agents, focusing on

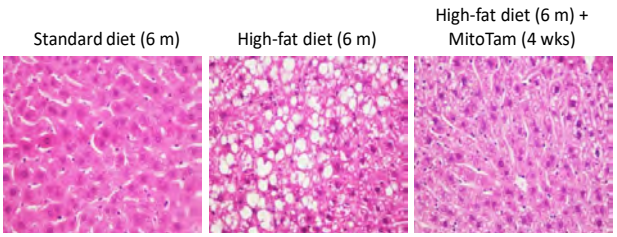


***Fig 9**. Mice were fed standard diet (SD) or high-fat diet (HFD) for 6 months, and the latter treated with MitoTam for 4 weeks. The images show formation of steatosis in HFD-fed mice normalized by MitoTam treatment.*

DHODH as a prospective broad-spectrum anti-cancer agent. Concerning re-purposing of MitoTam, we are finalizing a study in collaboration with Prof Haluzik (IKEM, Prague) showing unexpected activity of MitoTam against type 2 diabetes mellitus (Fig. 9). The manuscript will be submitted soon to Cell Metab. With respect to mitochondrial complex II and its wider role in the Krebs cycle and oxidative phosphorylation, we have discovered, in collaboration with Prof Pacak (National Institutes of Health, Bethesda, MD, USA), a new tumour suppressor, SUCLG2, which precedes CII in the Krebs cycle and considerably affects its function. We are preparing a relevant paper to be submitted in near future to Nat Genet. We will carry out a Phase 2 study with MitoTam and will be active-ly involved in the potential Phase 3 study planning. Overall, our vision is to carry out world-class basic research in the above topics that can be potentially utilized in the clinic.

9.3. Laboratory of Gene Expression

The main goal of our group for the next five years is to continue developing our expertise in single-cell and subcellular profiling with next-generation sequencing and proteomics technologies, and to apply these to a variety of long-term and newly initiated projects. Our projects of developmental biology will focused determination of the molecular mechanisms behind healing and regeneration. We

have introduced single-cell RNA-Seq, and this method will be a crucial part of our future work. It will be combined with extensive functional analysis and validation. We will also continue in spatiotemporal expression analysis using animal models covering a broad range of evolutionary trees from fishes and amphibians to mammals including human oocytes. In the field of neurobiology, we will continue in the projects that started in the previous period. We will study the role of miRNA in central nervous system injury and regeneration or the role of glial cells in the progression of amyotrophic lateral sclerosis. We will also initiate studies that were recently funded: the function of glial TRPV4 channels in brain oedema formation and post-ischemic regeneration and characterization of astrocyte nanofilament system in Alexander disease. We have recently purchased a new instrument, Chromium, from 10xGenomics, which extends the specialization of our group in single-cell analysis. We plan to grow our exper-tise in this field and its upcoming attractive branches such as spatial transcriptomics. We maintain collaboration with the TATAA Biocenter in organization of hands-on training courses in different aspects of molecular analyses from sample preparation, quality assessment, qPCR and NGS profiling, to data analysis.

9.4. Laboratory of Molecular Pathogenetics

We plan to continue our research by focusing on three areas. First, we will investigate the effects of diabetes and Hif1a mutation on the sympathetic system, specifically cardiac innervation, and the developing heart. For this purpose, we plan to submit a grant proposal to investigate these effects and a possible link to cardiac pathologies. Together with Prof Semenza (Johns Hopkins University School of Medicine), Prof Benes (EMBL Heidelberg) and Prof Kolar (Institute of Physiology CAS), we will also establish the role of HIF-1 in molecular and functional changes in association with heart dysfunction. Second, in collaboration with Prof Fritzsch (University of Iowa, USA) and Prof Syka (Institute of Experimental Medicine, CAS), we will continue our re-search on neurosensory development, auditory system, and hearing loss. Specifically, we plan to show the ISL1 function in the neuronal development of the inner ear. Using single-cell RNAseq, we will establish at the single cell level how neurons are affected by elimination of Isl1. Third, we have established a new line of research and received funding in collaboration with Prof Saudek (IKEM) to investigate the roles of ISL1 and NEUROD1 in pancreas development and in predisposition to diabetes mellitus.

9.5. Laboratory of Tumour Resistance

In the coming years, we plan to continue the major research topics of our laboratory, i.e., cancer resistance and iron metabolism. Currently, we are developing novel promising iron chelators that are targeted to mitochondria as crucial organelles responsible for the supply of both biologically utilized forms of iron, the FeS clusters and haem. The novel compounds show profound cytostatic and cytotoxic effects on cancer cells while sparing non-malignant cells (manuscript submitted to EMBO Mol Med). We aim to continue our research on molecular mechanisms that underlie tamoxifen-resistant cells and would like to extend our model to paclitaxel-resistant cells. We also plan to continue our work on interesting targets that are deregulated in cancer cells and regulate iron metabolism such as ABCB10 and QSOX1. Furthermore, we aim to investigate the regulation of systemic iron metabolism, in particular we will focus on the ERFE protein since we have promising data suggesting that its function is regulated by glycosylation; therefore, we will explore this topic further.

The future plans of the five laboratories of Team 1 are highly innovative and are bound to deliver ground-breaking results touching on the very basics of cell and molecular biology, greatly enriching our fundamental scientific knowledge, also branching to development and establishment of diagnostic and therapeutic approaches relevant to some of the most vexing pathologies of industrialized countries with potential overwhelming socio-economic impact.

10. Pedagogical activity

Number of semestral lectures, seminars and courses 2015-2019

Name of university	Lectured by	Title of the lecture	Bachelor	Master	Doctoral
Charles Univ, Faculty of Sci	Peknicova J	Molecular Mechanisms of Fe production		5	5
Griffith University, Qld, Australia	Neuzil J	Macromolecular and Cellular Biochemistry	5		
Griffith University, Qld, Australia	Neuzil J	Molecular Medicine	5		
Charles Univ, Faculty of Sci	Andera L	Molecular Mechanisms of Apoptosis		5	5
Charles Univ, Faculty of Sci	Šindelka R.	Genomic and Diagnostic Techniques	5	5	5
Charles Univ, Faculty of Sci	Šindelka R. Valihrach L.	Single Cell Gene Expression Analysis	1	1	1
CULS, Dpt. Vet Sciences	Šimoník O.	Management of Reproduction (selected practical lectures)		4	
CULS, Dpt. Vet Sciences	Šimoník O.	Veterinary Care of Animals	6		
Charles Univ, Faculty of Sci	Postlerová P.	Biochemistry of Mammalian Reproduction		5	5
CULS, Dpt. Vet Sciences	Postlerová P.	Cell Biology		5	
Charles Univ, Faculty of Sci	Frolíková M. Komrsková K. Postlerová P.	Physiology of Gametes and Fertilization		1	
Charles Univ, Faculty of Sci	Frolíková M. Komrsková K. Postlerová P	Methodology of Work with Gametes		1	
Charles Univ, Faculty of Sci	Komrsková K.	Animal Biology	5		
Charles Univ, Faculty of Sci	Šebková N.	Cell Biology for Geobiologists	4		
Charles Univ, Faculty of Sci	Šebková N.	Cell Biology for teachers	4		
Charles Univ, Faculty of Sci	Šebková N.	Cell Biology - a practical course	4		
Charles Univ, Faculty of Sci	Šebková N.	Developmental Biology - a practical course	4		

Supervision of students

Type of study	**No. of supervisors**	**No. of consultants**	**Theses defended 2015-2019**
Bachelor	28	3	18
Master	44	10	28
Doctoral	38	7	15

11. Participation of PhD students in the outputs

In our Team, we are committed to involvement of PhD students, in particular in activities of our constituent laboratories such that students actively carry out their projects including setting up and utilizing cutting-edge methodologies, and are instrumental for data interpretation and writing of manuscripts. In many cases, senior PhD student provide supervision, in particular leadership in tuition of methodology, etc., to junior PhD students and Master degree students.

All PhD students participate in the preparation of grant applications. Many of our PhD students have received grants from the Grant Agency of Charles University (GAUK) to support their own research projects. The following list represents two publications from each laboratory with PhD students as first authors.

References

(Abaffy et al., 2019)

(Bajzikova et al., 2019)

(Bosakova et al., 2018)

(Cerychova et al., 2018)

(Dostalova et al., 2017)

(Lettlova et al., 2018)

(Macova et al., 2019)

(Rohlenova et al., 2017)

(Tomkova et al., 2019)

(Zucha et al., 2019)

12. Involvement in the research centres with universities

Team 1 is an integral part of the international scientific centre BIOCEV, joint research facility of the Academy of Sciences and Charles University. Research and development performed in BIOCEV is focused on selected areas of biotechnologies and biomedicine. The scientific scope of BIOCEV has been divided into five research programmes, each of them dealing with a number of separate research projects. Team 1 is responsible for solving Program 5 “Development of Diagnostic and Therapeutic Procedures”.

In addition, individual laboratories cooperate with a number of other universities, in particular within joint research projects and are actively involved in the education of students.

13. Participation of the team members in activities of scientific community

Team members participate as reviewers for journals in their field of expertise.

Pěknicová Jana

- Chairman of the Council of the Institute of Biotechnology (2008 – present)
- Member of the Editorial Board of the Journal of Reproductive Biology and Endocrinology (2011 – present)
- Member of the Editorial Board of Bioprospect (2008 – present)
- Member of the Scientific Board of the Czech Science Foundation (2010-2014)
- Member of the Scientific Board of the Faculty of Fisheries and Protection of Waters, of the Univ. South Bohemia (2010-2017)
- Member of the Council of the Institute of Animal Physiology and Genetics (2012-2016)
- Member of the Board of Developmental and Cell Biology, Charles University, Prague (2008-present)
- Grant Reviewer for Czech Science Foundation, Grant Agency of Charles University, Grant Agency of the University of South Bohemia, Slovak Grant Agency

Komrsková Kateřina (Dvořáková-Hortová K.)

- Member of an evaluation board of the Czech Science Foundation
- Member of the BIOCEV Ethics Committee
- Member of the Coordination Board of Doctoral Study Programmes in Biomedicine for Charles University and Czech Academy of Sciences
- Expert Evaluator: European Research Council (ERC); Research, Development and Innovation Council (VaVaI), Government of the Czech Republic
- Grant Reviewer: Polish Grant Agency; Grant Agency of Charles University

Jonáková Věra

- Member of the Board of Developmental and Cell Biology, Charles University, Prague (2008-2019)

Pavlínková Gabriela

- Expert Evaluator of calls FP7-PEOPLE, FP7-Health, H20/20: IMI (Innovative Medicines Initiative), FET-OPEN, MSCA-IF, EIC-FTI
- Member of the Editorial Board of Scientific Reports (2018-present)
- Member of the Council of the Institute of Biotechnology (2018-present)
- Member of the Council of BIOCEV and BIOCEV Management Board (2009 – present)
- Scientific Evaluator for the Czech Science Foundation (2015-2020)
- Member of the Council for Foreign Relations, the Czech Academy of Sciences (2017-present)
- Member of the Academic Assembly of the Czech Academy of Sciences (2017- present)

Neužil Jiří

- Member of the Society for Free Radical Research
- President of the Society for Free Radical Research 2016-2018
- Member of the Cell Death Society and the Heart Research Society
- Vice-Chairman of the Council of the Institute of Biotechnology (2015-2018)
- Member of the Council of the Institute of Biotechnology (2019-present)
- Member of the Editorial Board of Mol Nutr Food Res, Oncol Res, BMC Cancer, Cell Commun Adhesion, Recent Patent Reviews Anti-Cancer Drug Discovery, Mitochondrion, Front Oncol
- Grant Reviewer for the Czech Science Foundation, Australian Research Council, National Health and Medical Research Council (Australia), VEGA, Swiss Science Foundation, etc.
- Founder of the biannual series of conferences Mitochondria, Apoptosis and Cancer (MAC), with MAC'09 in Prague, MAC'11 in Singapore, MAC'13 in Stockholm, MAC'15 in Frankfurt, MAC'17 in Bled, MAC'19 in Prague, MAC'21 in Singapore

- Chair of international conference of Mitochondria, Apoptosis and Cancer MAC'19 (Prague); member of the organizing committee of MAC'15 (Frankfurt), MAC'17 (Bled, Slovenia)
- Member of the organizing committee of World Congress on Mitochondrial Targeting in Berlin (2015, 2016, 2017).

Anděra Ladislav

- Member of the European Cell Death Organization
- Member of the Accommodation Committee of the CAS
- Member of the PhD Commission for Biomedicine (in Prague, České Budějovice)
- Grant reviewer for the Ministry of Education, Youth and Sports, Grant Agency of Charles University.

Kubista Mikael

- Scientific advisor to Roche
- Scientific advisor to ThermoFisher
- Scientific advisor to Qiagen
- Scientific advisor to Bio-Rad
- Member of the Scientific Advisory Board of InSilixa Inc.
- Member of the Scientific Advisory Council of Genetic Engineering News
- Expert advisor for the European Commission Research Directorate General
- Special consultant in the Life Science area for Arthur D. Little Inc.
- Advisor for the United Nations Educational Scientific and Cultural Organization (UNESCO) and Member of the scientific advisory board for the International Biotechnology Research in Tripoli, Libya (a UNESCO effort)
- Editor of Scientific Reports, Nature Publishing group
- Founding Editor of Biomolecular Detection and Quantification

Truksa Jaroslav

- Member of the International BioIron Society, European Iron Club and European Cell Proliferation Society
- Member of the Council of the Institute of Biotechnology (2013 - 2019)
- Grant reviewer for the Ministry of Education, Youth and Sports, Grant Agency of Charles University

14. Organized conferences and workshops

Neužil J.:

- Chief Organizer of Annual Conference of the Society for Free Radical Research (Australasia Branch), Gold Coast, Qld, Australia, December 2015
- Chief Organizer of international biannual conference on Mitochondria, Apoptosis and Cancer (MAC'19) in Prague, September 2019.

Kubista M:

- Co-organizer of TATAA courses (Hands-on qPCR, Experimental Design and Data Analysis, MicroRNA), at least twice a year
- Co-organizer of international meeting Single Cell Europe with 180 participants (2018)

Pěknicová J.:

- Co-organizer of the Symposium of Immunology and Biology of Reproduction with International Participation, every year (2015-2019).

15. Invited lectures and earned awards

Komrsková K:

- Invited talk at the University of Padova, Italy (2019)
- Invited guest speaker for TMU-UoN Symposium, Taipei, Taiwan (2018)
- Invited talk at Hudson Inst., Monash University and University of Queensland, Melbourne, Australia (2018)
- Invited plenary speaker at ARE, Asociace reprodukční embryologie, CR (2017)
- Guest speaker at the Annual Meeting of the German Society of Andrology, Physiology of Reproduction section, Saarbrucken, Germany (2016)
- Guest speaker and panellist, opening of the Life Sciences Film Festival Suchdol, Czech Republic (2015)

Pěknicová J.:

- Invited plenary speaker for the 14th International Symposium for Immunology of Reproduction. May, 2015, Varna, Bulgaria (Impact of endocrine disruptors on male reproductive and epigenetic parameters in a trans-generational study of mice)
- Invited talk at XXVth Biochemical Congress (2016), Prague (Evaluation of the expression selected acrosomal proteins in men with normal and pathological proteins using monoclonal antibodies)
- Invited plenary speaker for the 15th International Symposium for Immunology of Reproduction, 2018, Varna, Bulgaria (Multigenerational effect of diabetes mellitus on mammalian reproductive parameters)

Jonáková V.:

- Invited plenary speaker for the 14th International Symposium for Immunology of Reproduction, 2015, Varna, Bulgaria (Acrosin inhibitors and their regulation by the ubiquitin-proteasome system in boar reproductive tract)
- Invited plenary speaker for the 15th International Symposium for Immunology of Reproduction, 2018, Varna, Bulgaria (Study of regulatory mechanisms of ubiquitin-proteasome system in reproduction)

Neuzil J:

- Invited talks in a number of international institutions, including the University of Padova (Italy), Institute Pasteur (Paris, France), University of Paris Sud (France), University of Lubeck (Germany), University of Southern Denmark, University of Copenhagen (Denmark), Karolinska Institutet (Stockholm, Sweden), Jozef Stefan Institute (Ljubljana, Slovenia), Seoul National University (South Korea), Taibei Medical University (Taiwan), Taiwan National University (Taibei, Taiwan), University of Western Australia (Perth, Australia), University of Sydney (Australia), Malaghan Institute (Wellington, New

Zealand), Otago University (Christchurch, New Zealand), University of Heidelberg (Germany), Institute of Enzymology (Budapest, Hungary), Commenius University, (Bratislava, Slovakia)

- Invited/Keynote speaker at numerous international conferences, including a keynote/invited speaker at a number of international conferences, such as the International conference on Membrane Redox System (Wellington, New Zealand), World Congress on Targeting Mitochondria (Berlin, Germany), International Conference on Heme Oxygenase (Prague), etc.
- Awarded the Medal of the Czecho-Slovak Society for Cell Biology (2019)

Pavlínková G.:

- Invited speaker at the 2nd International Munich ROS Meeting July 6-8, 2018 German Heart Centre Munich, Germany (Combinatorial effects of diabetes and Hif1a mutation on cardiovascular development and function).

Kubista M.:

- Members of the laboratory are invited to numerous talks (~ 10 every year – international conferences, collaborating partners) in the field of gene expression analysis and its application on various biological and medical questions.

Truksa J.:

- Invited talk at the European Iron Club 2018 meeting, Zurich, Switzerland, and MAC19 symposium, Prague, Czech Republic
- Awarded Kellner Family Foundation Science Award for research project “Expression and Regulation of Multi-Drug Resistance Proteins in Tumour-Initiating Cells (TICs)”.

16. Participation in large collaborations

Participation in large collaborations is important for bringing together a critical mass of researchers to tackle a certain, often more comprehensive problem. These collaborations are organised on the bases of programme grants provided by research funders, or are an incentive of individual senior researchers. An example of a large collaboration within our Team is a project by the Laboratory of Molecular Therapy that has been conducting, since about 2013, a project examining the molecular mechanism, regulation and functional impact of horizontal transfer of mitochondria in cancer. A prime example is epitomized by their recent publication in Cell Metab (Bajzikova et al., 2019) that involves 50 co-authors from 15 individual laboratories from the Czech Republic and other countries (including those in North America, Europe, Asia, and Australia/New Zealand).

The Laboratory of Gene Expression maintains collaboration with the TATAA Biocenter in organization of hands-on training courses in different aspects of molecular analyses from sample preparation, quality assessment, qPCR and NGS profiling, to data analysis. Together, they also organized international conference Single-Cell Europe with more than 150 participants in 2018. The Laboratory is also involved in extensive international cooperation within the European Joint Programme on Rare Diseases (EJP RD, 2020-2023) - collaboration with five laboratories across Europe (Netherlands, Sweden, Israel, Spain) and two patient organizations (Luxembourg, Netherlands), and is one of a group of laboratories focusing on the astrocyte nanofilament system in Alexander disease – from molecules to function, uncovering new leads for therapy.

17. Outreach activities

Source	Date	Title/Employee
IBT Brochure	2019	Brochure about IBT: 2015 - 2019
iRozhlas	30.11.19	Cancer medicine can also treat diabetes IKEM/Neužil J.
Panorama 21. století	11/2019	The latest advance in cancer treatment – Neužil J.
Český rozhlas: Plus	22.10.2019	Will the cure for cancer be made by Czech scientists? –Neužil J.
ČT: Studio ČT24	7.10.2019	Nobel Prize Awards (reactions, feedback) – Pavlínková G.
Prima TV - YouTube	25.9.2019	Jiří Neužil - Show Jana Krause
ČT: Studio 6	20.9.2019	Scientists are testing a new anticancer substance. Neužil J.
Český rozhlas: Plus	12.9.2019	The antitumor substance of Czech scientists is promising. But it is still far to practical application. Neužil J.
ČT: Studio ČT24	19.6.2019	Research on hearing loss – Pavlínková G.
ČT24 Věda	16.6.2019	Promising anti-cancer agent. – Stursa J., Werner L.
Scientific American	3-4/2019	Institute of Biotechnology – special section: Cancer Cells as Mitochondria Thieves. Neužil J.
Věda a výzkum.cz	15.3.2019	Unites States – a key partner of Czech research.
seznamzpravy.cz	15.3.2019	Why do Czech billionaires invest hundreds of millions of crowns in biotechnology?
seznamzpravy.cz	11.3.2019	„We could improve cancer treatment“ - investor, Komárek K., senior.
Vesmír	4.3.2019	Why do cancer cells steal mitochondria? Neužil J., Rohlena J.
ČT: Studio ČT24	25.2.2019	Scientists examining hearing disorders – Pavlínková G.
BIOCEV press release	20.2.2019	Hearing without distinction of sound frequencies: Genetic mutation showing limited ability to reorganize the central auditory pathway – Pavlínková G.
Radio Praha (in English)	14.2.2019	New hope for cancer patients: drug in clinical testing makes cancer cells self-destruct – Neužil J.
Institut Pasteur Website	28.1.2019	A new biochemical pathway implicated in the proliferation of cancer cells. Neužil J.
Český rozhlas 2	24.1.2019	We are already testing cancer medicine on patients, but it won´t be a year away, says biochemist and biologist. Neužil J.
Vesmír	7.1.2019	From stoker to manager: The story of the respiratory complex II. - Rohlena J., Neužil J.
Český rozhlas: Plus	21.12.2018	Science and technology events: substance from Czech laboratories.
ČTK (České noviny)	5.12.2018	Scientists have revealed the importance of respiration in cancer cells. Neužil J.
Česká televize: Babylon	1.12.2018	Jiří Neužil has interconnected two continents.
Česká televize: Fokus VM	20.11.2018	Treatment of the future: MitoTam. Neužil J.
Novinky.cz	31.10.2018	Scientific cooperation between Czechs and Americans. The MEYS will support 46 projects.
SCIENCEmag.cz	16.7.2018	Does iron help tumour “super-cells” escape treatment? Truksa J.
Český Rozhlas: iRozhlas	24.6.2018	Czech scientists are testing a new substance against breast cancer. It can make a tumour suicide. Neužil J.
Česká televize: Události	14.6.2018	A new cancer drug is being tested. Neužil J.
SCIENCEmag.cz	24.5.2018	MitoTam targets tumour mitochondria. Neužil J.
týden.cz	22.5.2018	Scientists have discovered a substance that could help cancer therapy. Neužil J.
Dolnobřežanský rozkvět	3/2018	News from STAR – BIOCEV –Neužil J.
A Věda a výzkum	1/2018	We will not die of infertility – Pěknicová J., Pavlínková G.
Česká věda	3/2018	Smaller and even smaller RNA (video) - Valihrach L.
Enviweb.cz	18. 2. 2018	Diabetes affects the reproduction of mammals, including man – Pěknicová J.
Parlamentní listy	28. 12. 2017	Academy of Sciences: Diabetes affects the reproduction of mammals, including man – Pěknicová J, Pavlínková G.
ČT24 Studio	18.12.2017	Influence of diabetes on fertility - Pavlínková G., Pěknicová J.

ČT24 Věda	15. 12. 2017	Beware of diabetes, it affects the reproduction of mammals. Including man, reports Czech research – Pěknicová J., Pavlínková G.
Vesmír 96	11/2017	Mitochondria, a new target for cancer therapy - Rohlenová K., Rohlena J., Neužil J..
Parlamentní listy	22. 11. 2017	President of the Academy of Sciences on tour: Three Institutes, Three Days.
Youtube.com (TVT 2017)	8. 11. 2017	New approaches to early diagnosis and improvement of sperm quality – Komrsková K.
Youtube.com (TVT 2017)	8. 11. 2017	Can parents´ diabetes mellitus negatively affect their offspring? – Bohuslavová R.
ČT Studio 6	4. 11. 2017	The first baby from the tube celebrates 35 years – Pěknicová J.
Metro	20. 9. 2017	One day by a phenogenomic!
A Věda a výzkum	3/2017	The Preclinical Testing Centre for potential drugs is open. Neužil J.
Gate2Biotech	4. 8. 2017	The Czech-Swedish team has developed a new procedure for accurate determination of microRNAs – Kubista M.
EkonTech.cz	26. 7. 2017	The new substance destroys cancer. Our MitoTam is promising, the study begins on people“ – Rohlenová K.
ScienceMag.cz	13. 7. 2017	A new technique for the analysis of small RNA molecules – Kubista M.
Interview	6/2017	Make cancer suicide. – Rohlenová K., Neužil J.
21. století	4/2017	Czech scientists have a cure for cancer! Neužil J.
Březanský zpravodaj	3/2017	Cancer cell – the world for itself. Neužil J.
Lidové noviny Relax	8. 3. 2017	Obesity or high oestrogen levels will also affect breast cancer.
Česká televize: Události	2. 3. 2017	The process of introducing new drugs into practice. Rohlenová K., Neužil J.
5+2	10. 2. 2017	We will beat breast cancer, Czech scientists believe. Neužil J.
DVTV	2. 2. 2017	We take energy from tumours, our medicine could work elsewhere than in breast cancer, Neuzil says.
Český rozhlas 2	27.1.2017	Jiří Drahoš: When will the new Czech cure for breast cancer reach patients?
ČT24 Věda	22. 1. 2017	Czech scientists are developing a new substance against breast cancer. Neužil J., Rohlenová K.
ČT Studio 6	20. 1. 2017	A new anti-breast cancer agent. Neužil J., Rohlenová K.
ČRo Plus	19. 1. 2017	Breast cancer substance from Czech scientists forces tumour cells to suicide. Neužil J.
Novinky.cz	19. 1. 2017	Czech scientist´s drug, which forces cancer cells to “suicide”, is heading for tests. Neužil J.
Technický týdeník	19. 1. 2017	BIOCEV scientists have forced cancer cells to destroy themselves. Neužil J., Rohlenová K.
21. století - online	19. 1. 2017	Czech scientists are on the trail to cancer medicine. Neužil J.
Aha online	19. 1. 2017	A major Czech discovery: A new cure for breast cancer! Neužil J.
iRozhlas	18. 1. 2017	A breakthrough in breast cancer treatment? Czech scientists have developed a substance that forces cancer-causing cells to suicide. Neužil J.
Medical Tribune.cz	18. 1. 2017	BIOCEV scientists have forced tumour cells to destroy themselves. Neužil J.
Expats.cz	18. 1. 2017	Czech Scientists Develop Breakthrough Breast Cancer Drug. Neužil J.
TV Noviny SK	18. 1. 2017	Hope for millions of women. Czech scientists have discovered the Achilles‘ heel of breast cancer. Neužil J.
Lidové noviny	17. 1. 2017	A new hope for women suffering from breast cancer. Neužil J.
Technet.cz	17. 1. 2017	Czech scientists have “choked” breast cancer with a new substance. They plan human tests. Neužil J., Štursa J.
Blesk.cz	17. 1. 2017	Czechs make cancer suicide: Scientists want to test the new medicine on people. Neužil J.
Lidovky.cz	16. 1. 2017	Czech scientists have developed a breakthrough remedy for aggressive breast cancer. Neužil J.
Česká televize - Věda	5. 12. 2016	Nanodiamonds against diabetes and key for the treatment of male infertility. How Czech scientists change medicine. Komrsková K.

Česká televize - Události	2. 12. 2016	Promising Czech research, Komrsková K.
Literární noviny	9/2016	Talking to Professors: We attack cancer from the inside – Neužil J.
Scientific American	6/2016	Institute of Biotechnology – special section
Forbes	4/2016	Komarek's secret
Atlas of Science	15. 11. 2015	Maternal diabetes negatively affects the development of embryonic heart - Pavlínková G., Bohuslavova R.
scienceworld.cz	24. 6. 2015	Uneven distribution of microRNAs – a new mechanism affecting asymmetric cell division – Kubista M..
Ekonom (č. 17/2015)	23. 4. 2015	Billionaires are attracted by biotechnology. Neužil J.
Akademický bulletin	2/2015	Robber cells. Neužil J.
Gate2Biotech	2. 2. 2015	Unique ability of tumour cells. Neužil J.
Nature Reviews Cancer	2/2015	The mitochondria thief –Neužil J.
Lidové noviny	31. 1. 2015	Cancer steals DNA. Neužil J.
EuroZprávy.cz	28. 1. 2015	Breakthrough discovery of Czech scientists: Cancer is more resistant than we thought. Neužil J.
technet.cz	28. 1. 2015	"Genetically modified" cancer steals DNA from healthy cells. Neužil J.
deník.cz	28. 1. 2015	Czech and Australian scientists have found out why cells can form tumours. Neuzil J.
ČRo Radiožurnál	28. 1. 2015	How does cancer develop? Czech scientists found out why cells can form tumours. (audio) Neužil J.
týden.cz	28. 1. 2015	Czech and Australian scientists have found out why cells can form tumours. Neužil J.
Aktuálně.cz	28. 1. 2015	Scientists have revealed the weakness of cancer, the Czech investigators also participated. Neužil J.
Regionální noviny	28. 1. 2015	The team led by Jiri Neuzil described the unique ability of tumour cells "to breathe".
ČT24	28. 1. 2015	How does a tumour develop? According to scientists, cancer cells "steal" functional mitochondria. Neužil J.
Akademický bulletin	22. 1. 2015	Cell robberies. Neužil J.
Science and Technology Week	2015 - 2019	IBT organizes an Open Door Day in November every year.

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