Information on the activity of the institute

1. The mission of the Institute of Biotechnology of the Czech Academy of Sciences

- *Our vision* is achieving breakthrough results created by curiosity driven research of the molecular mechanisms of biological phenomena with high a socio-economic impact.
- *Our mission* is to gain new knowledge on molecular mechanisms of pathologies with considerable impact on population health; to develop new methods of protein engineering and structural biology that enable understanding of the functioning of biological molecular systems and open new ways to modify them.
- *Our strategy*:

- To support excellence of curiosity driven research because excellence opens ways to great discoveries and new applications.
    - The laboratories operate quite independently and laboratory heads have a lot of freedom to choose research topics and the strategies to tackle them, but they are also held accountable for the quality and quantity of the results.
- To identify projects of the highest application potential and choose effective ways of their commercial implementation.
    - Implementation of the research results is an integral part of our work.
- To steer the quality of our work and optimize the allocation of institutional resources we perform internal evaluation of all research laboratories and scientists based on their publication and application performance.
- General directions of our research topics are navigated by the internal Board of IBT and from year 2020 by a newly formed international Scientific Advisory Board (SAB).
- Great ideas feed on smart, motivated, and enthusiastic people, cutting edge equipment and stable financial support. Therefore:
    - all laboratories are encouraged to collaborate on local, national, and international levels to keep the flow of fresh ideas and new impulses for our work;
    - we build on the success of our massive involvement in the conceptualization (2007-2009), designing (2010-2013), and building (2014-2015) the research center BIOCEV. IBT has become a core institution of BIOCEV, an excellently equipped hub for national and international collaborations.
- We understand the importance of and take part in the service to the scientific community, pedagogical activities, popularization, and organization of conferences, workshops, and courses.

1.1. The institute organization

IBT currently (end of May 2020) consists of nine senior and two junior laboratories, three service laboratories and department of administrative and technical services. The laboratories work in two complementary research branches that are referred to as Team 1 and Team 2 further in the report. This duality reflects the history of the institute and does not preclude cooperation between laboratories within or between the teams. The research directions of Team 1 and 2 are methodologically complementary and their collaboration enriches each other for the benefit of the entire institute.

Team 1 comprises five laboratories, four senior, one junior. All labs are focusing on understanding the molecular and cellular bases of a variety of pathological states. The common denominator of all projects addressed by Team 1 is the pathological state of the cell and uncovering the molecular mechanisms causing this state. We profile selected genes, detect changes in the localization and modification of relevant proteins, and identify other molecules that are involved in the initiation and progression of the pathological state.

Team 2 has six laboratories, four senior, two junior. The main objective of the team is to mechanistically explain fundamental biological processes with potential applications of the results in the diagnosis and treatment of diseases. We study the mechanisms underlying intermolecular interactions in biomolecular systems and, in a broader sense, the relationship between the biomolecular structure and function. The studied molecular systems are produced by advanced techniques of molecular biology and protein engineering; their dynamics, structure, stability, and activity are determined by the state-of-the-art structural and biophysical experimental and computational methods.

The service laboratories are not formally part of the Teams but they are important for our research. There are three: The Centre of Molecular Structure provides for the needs of the Czech and international community in techniques of structure biology and protein characterization and is a part of the Czech distributed Instruct-ERIC infrastructure. The Gene Core is a leading European service provider in the field of gene expression, and the Service Technology Laboratory is oriented towards medicinal chemistry and development of promising potential drugs in the preclinical and early clinical stages. All three service laboratories are equipped with cutting edge instrumentation.

The research activities, overview of the teams as well as the budget of IBT are concisely summarized in a brochure available as a pdf file from IBT website or in paper copy. The most recent information can also be found at the institute website ibt.cas.cz.

1.2. The institute future

We are convinced that the above outline of the mission of the Institute of Biotechnology of the Czech Academy of Sciences and its general principles of operation are correct and we do not expect significant changes in the strategies to strive for scientific excellence. Within the 12 years of IBT´s existence, it has grown from humble beginnings into one of the most successful institutes of the Czech Academy of Sciences in terms of our scientific results, application potential, and financial security.

The institute will further support collaborations of the individual laboratories with national and foreign institutes and laboratories. We need to more actively seek larger scale collaborations and should be more actively looking for opportunities to submit large projects with foreign partners. We must continue to play an active role in the work of Pan-European infrastructure projects such as Instruct-ERIC and ELIXIR. In this context, the establishment of the international Scientific Advisory Board (SAB) will be important for the future of IBT

The institute, its management as well as the employees are all united in the effort to strengthen the prestige and impact of IBT in the Czech Republic, but mainly on an international scale, because only the world-wide research and development community provides the strict indicator for the quality of our scientific results.

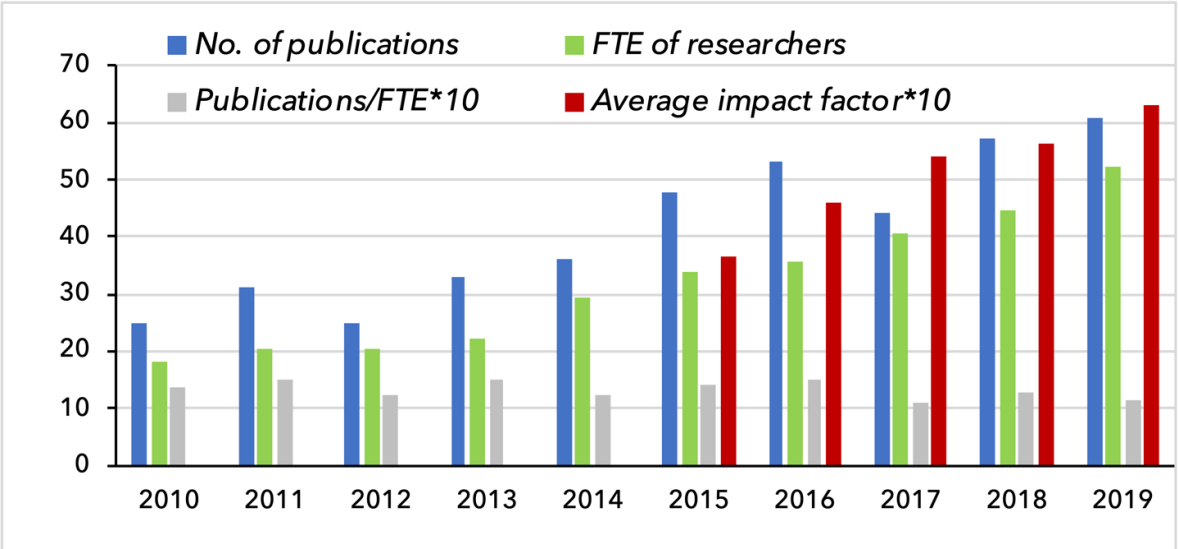
2. Description of the main research directions investigated by the institute

In this chapter, we first outline the institute´s output in scientific journals and applications and briefly discuss how it is evolving in time and its main components. Then we highlight the main research directions and draft the research interests of both Teams with citing the key references.

2.1. Overall situation

IBT was founded in 2008 and has evolved into a well-established member of the Czech Academy of Sciences since then. Since its beginnings, the research strategy followed two branches reflected in this report as activities of Team 1 and Team 2. The current organizational structure of the institute, with nine senior laboratories, two junior laboratories and three infrastructure (service) laboratories, is functional and sustainable. The evaluated period between years 2015 and 2019 can be characterized as stabilization of IBT with two new junior laboratories created. Together with the successful relocation from the old and limiting premises in the bio-medical campus Krc to the new BIOCEV center in Fall 2015 led to a gradual and measurable growth of the scientific output.

The scientific output of IBT is summarized by the histogram below for years 2010 - 2019. We do not include data for years 2008 and 2009 because they report on the initial, basically preparatory, phase of IBT's development. The graph shows the absolute number of papers published in impacted journals (blue), the average number of full time equivalents of researchers in a given year (green), the fraction of the above two numbers multiplied by 10 (grey), and finally the average impact factor of the journals where we published in a given year, again multiplied by 10 (red). The last two numbers were multiplied by 10 to keep data on approximately the same scale.



What does the graph tell us? First of all, the number of publications steadily growths during the whole ten-year period. Even when the average number of published papers divided by the numbers of FTEs of scientists (grey bars in the graph above) is basically constant, does not grow, the impact of our research has increased. We estimate it as the average impact factor of journals where we published (red bars), which grew from less than 4 in year 2015 to more than 6 in year 2019. This is quite a significant jump.

In addition, the histogram above does not include data on our outputs classified as transfer of knowledge, which contribute to the productivity of our research teams. IBT's striving for scientific excellence has been therefore accompanied by an increasing output of applications. Most of these results have had commercial benefits and they have grown during the last five years in both quantity and quality. It is detailed in Chapter 10 Research for Practice. In the evaluated period, we filed 8 patents and obtained several tens of other applied results. The most significant result in this context is

the discovery of a new class of potential anticancer drugs targeting mitochondria with the most promising compound, MitoTam. The project has attracted the venture capital and the compound MitoTam is currently being under scrutiny in clinical trials.

To get a more detailed view of IBT's research output in general during years 2015-2019, we point to the list of publications, books, and applied results the IBT Teams 1 and 2 submitted in Phase I of the evaluation.

The most important component of all institute's attributes is its staff. Our HR policy is discussed in Chapter 4 and 5 below. Let us just state here that the age structure of IBT employees is very promising, and we have a very good proportion of older experienced scientists with a PhD title (64 and students, mostly doctoral (the total number of PhD students employed in the institute is 42).

IBT benefits from its participation in the BIOCEV center. The newly established research center has despite its short duration acquired a great national and international reputation. The center as a joint project of six institutes of the Czech Academy of Sciences and two faculties of the Charles university is a great place for broad, interdisciplinary collaborations, enables easy access to the state of the art equipment in several areas of life sciences. The number of scientists, students, and technicians working in BIOCEV is sufficient to master various methodologies with top level expertise and the spectrum of the methodologies available *in situ* allows for synergies between different approaches and certain flexibility in the research plans. The staff of the institute has excellent equipment at its disposal, whether it is owned by the IBT or partner institutes of the Czech Academy of Sciences, or by both faculties of the Charles University. In addition, our affiliation with the BIOCEV project and partnership with the Faculty of Science and First Faculty of Medicine of the Charles University provides a great opportunity to attract students and the laboratories of both Teams have been successful in finding good graduate and undergraduate students as well as students of European Erasmus projects. This is essential for the fulfillment of IBT research tasks but it also fulfills an important function of IBT to train the educated and confident generation of future scientists and teachers. Especially Team 1 appreciates the BIOCEV infrastructure Czech Center for Phenogenomics, CCP, which allows close collaboration on development of unique animal (mouse) models.

As already mentioned, the quality and sustainability of our research depends to a significant extent on the availability of service laboratories with top level equipment and a sufficient number of expert staff and correspondence between scientific ideas and their technical execution is essential. IBT itself operates three top level service laboratories: the Centre of Molecular Structure (CMS), Gene Core - Quantitative and Digital PCR and the Service Technology Laboratory. CMS is a state-of-the-art structural biological workplace and, thanks to close cooperation with structural biologists from CEITEC at Masaryk University (Brno), it has succeeded in obtaining the status of an international center of the Pan-European infrastructure Instruct-ERIC. Due to this status, CMS offers international courses and thus increases the visibility of IBT and attracts new projects. Gene Core - Quantitative and Digital PCR is a service laboratory with expertise in PCR techniques and single-cell techniques. Gene Core co-organizes international courses with the company TATAA Biocenter, which, in addition to the visibility, bring the institute new opportunities for cooperation. The Service Technology Laboratory is an organic chemistry laboratory with the staff possessing irreplaceable know-how for commercial development of potential drugs and for the preparation of their preclinical and clinical testing.

2.2. Highlights of the research directions of the institute

The IBT research can be categorized into several main directions as outlined below.

- Research of the mitochondrial energetics. This research direction emphasizes targeting cancer cells via their metabolism mainly by impeding the Complex I and by interfering with their iron metabolism. These efforts led to a fundamental discovery of the horizontal gene transfer of mitochondria between cells and to clinical trials of the compound MitoTam.
- Research projects in the field of developmental biology, transcriptional regulation during embryonic development, and development of the neuronal system in vertebrates. The research aims at identification of the disease predispositions evolving during early development of the

organisms extending to cancer research and diagnosis with aiming at potentially applicable results.
- Research of male reproductive molecular and subcellular parameters as markers of fertility disorders involved in sperm-egg fusion including detailed characterization of the dynamic rearrangement of cytoskeletal proteins and their partner proteins.
- New method development of RT-qPCR and implementation of high-throughput gene expression profiling and single-cell analysis using RNA-Seq.
- Protein engineering combining techniques of in vitro protein evolution and of computer modeling for targeted modulation of protein properties such as binding affinity to medically important proteins.
- Structure-function studies of proteins including structure-assisted drug design employing modern methods of biophysical and structural molecular analysis including X-ray crystallography.
- Dynamics of biomolecules and imaging of single molecules and force measurement techniques to uncover how the individual structural elements of the cytoskeleton mechanically cooperate to drive diverse cellular processes.
- Studies of the time dimension of biomolecular dynamics from ultra-short (fs) to medium (ms).
- Structural bioinformatics with unique know-how of nucleic acid structures.

2.3. Scientific profiles of the research laboratories of the Teams 1 and 2

The detailed scientific profiles of the Teams 1 and 2 and the constituting research laboratories are presented in part 3.4 of the evaluation report, here we just summarize research directions of both Teams and select the representative results that in our opinion document their excellent scientific quality and ability to remain leaders in their research areas. Importantly, our research is based on advanced methodological approaches and brings innovative ideas published in high quality journals as well as translational research with patents that are being transferred into the medical practice.

2.3.1. Team 1

The five research labs of Team 1 are engaged in cutting-edge basic research aimed at providing better understanding of the molecular mechanism of highly socio-economically challenging human pathologies with considerable impact on population health. The focus is to study genesis and progress of the selected pathologies at the subcellular and molecular levels on cell cultures and animal models and identify their relevant diagnostic biomarkers, to uncover novel functions of genes, detect the changes in the localization and modification of relevant proteins, and identify other molecules involved in the pathological states. An important output is identification of novel and efficient therapeutic approaches. 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.

Laboratory of Reproductive Biology, Head: Kateřina Komrsková

The main focus of the laboratory is on the molecular mechanisms of fertilization and specific sperm proteins that play a role in sperm maturation, sperm-egg interaction, and early embryo development. We proved the key role of trans-generational epigenetic de-regulation of microRNA expression induced by pollutants in germ cell differentiation. We detect sperm quality in patients with testicular cancer and diabetes mellitus and characterize sperm antibodies in infertile couples. The knowledge is utilized in development of new diagnostic tools for quality assessment and gamete selection for Centers of Assisted Reproduction.

(Vieweg et al., 2015)

(Frolikova et al., 2016)

(Frolikova et al., 2018)

Laboratory of Molecular Therapy, Head: Jiří Neužil

The 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. The group published 56 papers in the last five years.

(Tan et al., 2015)

(Bezawork-Geleta et al., 2018)

(Bajzikova et al., 2019)

Patent: Neužil, Jiří, Werner, L., Štursa, J. Tamoxifen derivatives for treatment of neoplastic diseases, especially with high HER2 protein level. J. Neužil, Institute of Biotechnology of the Czech Academy of Sciences, Smart Brain s.r.o., KKCG AG. 2018. Number of the patent folder: US9896466. Date of the patent award: 2020-02-20.

Laboratory of Gene Expression, Head: Michael Kubista

The laboratory is Europe's leading academic laboratory specialized in high-throughput gene expression profiling and single-cell analysis using real-time quantitative PCR (qPCR) and RNA-sequencing. We have several basic research projects in the field of developmental biology and stem cells, and applied projects in cancer and neurological research. We also develop methods and applications for nucleic acid analyses and we are active in the area of standardization. The group published more than 40 publications in peer-reviewed journals.

(Androvic et al., 2017)

(Stahlberg & Kubista, 2018)

(Valihrach et al., 2020)

Laboratory of Molecular Pathogenetics, Head: Gabriela Pavlínková

The research program of the laboratory is focused on transcriptional regulation during embryonic development, developmental programming, and identification of the molecular causes of disease predispositions, particularly diabetes and heart disease. 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 analyze the combinatorial effects of the environment and genetic mutations.

(Bohuslavova et al., 2017)

(Cerychova et al., 2018)

(Bohuslavova et al., 2019)

Laboratory of Tumor Resistance, Head: Jaroslav Truksa, junior laboratory

The main scientific topics of the laboratory are i) Understanding the molecular mechanisms that lead to the proliferation, resistance, and recurrent appearance of cancer cells. ii) Describing the biology of cancer stem cells with the interest targeted to their iron metabolism. iii) Developing new ways to affect cancer cells based on targeting their mitochondria and deregulating their iron metabolism. iv) Deciphering the molecular mechanisms that are responsible for the proper functioning of the iron metabolism throughout the body.

(Rychtarcikova et al., 2017)

(Lettlova et al., 2018)

(Tomkova et al., 2019)

2.3.2. Team 2

The main objective of the team is to mechanistically explain fundamental biological processes with potential applications of the results in the diagnosis and treatment of diseases. Our aim is to understand the mechanisms underlying intermolecular interactions in biomolecular systems and, in a broader sense, the relationship between the biomolecular structure and function. The studied molecular systems are produced by advanced techniques of molecular biology and protein engineering; their dynamics, structure, stability, and activity are determined by the state-of-the-art structural and biophysical experimental and computational methods.

Laboratory of structural biology, Head: Cyril Bařinka

We aspire to elucidate molecular details of the structure and function of several pharmaceutically important zinc-dependent hydrolases, including histone deacetylases and glutamate carboxypeptidases, from the single molecule level to their physiological roles in cellular environments. We also use protein engineering and structure-assisted drug discovery to develop macromolecules and small molecule ligands, respectively, that can be used as research tools and/or be advanced into clinical practice. A platform for heterologous expression and purification of recombinant proteins implemented in our laboratory is extensively used not only by us but also by a wide network of our collaborators and in our commercially oriented on-demand protein production.

(Novakova et al., 2016)

(Kutil et al., 2018)

(Kutil et al., 2019)

Laboratory of structure and function of biomolecules, Head: Jan Dohnálek

The laboratory applies integrative structural biology approaches to investigate new enzymes, receptors, and large molecular complexes with biotechnological or biomedical potential. The uncovered structure-function relationships explain basic biological functions and are applicable in nanotechnologies or in the fight against opportunistic human pathogens and diseases. Our structure-function studies of enzymes with biomedical and biotechnological potential have yielded results in three main directions: i) non-specific nucleases; ii) bilirubin oxidase; and iii) novel glycosidases. New enzymes for biotechnology are studied with a world leader in the field - Novozymes A/S.

(Trundová et al., 2018)

(Kovaľ & Dohnálek, 2018)

(Koval et al., 2019)

Laboratory of ligand engineering, Head: Petr Malý

The laboratory uses methods of directed evolution of proteins for the generation of unique collections of binding proteins targeted to human cytokines and their receptors, serum oncomarkers, bacterial toxins, and insoluble components of fibrin network. A special attention is paid to the development of “non-cognate ligands” of broadly neutralizing human antibodies identified as “protein prints” mimicking epitopes of virus-neutralizing antibodies to be used as promising immunogens for development of novel protective vaccines. By screening of highly complex combinatorial libraries we identified “protein prints” that can be used as strong immunogens for the stimulation of protective antibodies similar to those originally used as molecular targets.

(Mareckova et al., 2015)

(Hlavnickova et al., 2018)

(Petrokova et al., 2019)

Laboratory of biomolecular recognition, Head: Bohdan Schneider

We focus on understanding interactions driving the specific recognition between biomolecules with a potential diagnostic, medical, or biotechnological use. We apply experimental and computational

methods of protein engineering, structural biology, bioinformatics, and molecular modeling to study: i) cytokines and their receptors; ii) time-resolved biomolecular dynamic of light-inducible proteins; and iii) a bacterial transposase RAYT and the related REP DNA. We have a unique know-how in structural bioinformatics of nucleic acids. For more, please see the website biorecognition.structbio.org.

(Mikulecky et al., 2016)

(Schneider et al., 2017)

(Zahradnik et al., 2019)

Laboratory of structural bioinformatics of proteins, Head: Jiří Černý, junior laboratory

The laboratory concentrates on the development and application of structural alphabets for annotation, modeling, model building, validation, and refinement of experimental structures and computer models of proteins and nucleic acids. It also contributes to a deeper understanding of structural and functional features of biologically relevant molecules and their interactions by developing novel computational methods and procedures for modeling of biomolecules and their complexes. It is involved in several collaborations on projects covering structural bioinformatics and molecular modeling of biomolecules or small drug-like molecules with both Teams of IBT as well as outside.

(Cerny et al., 2016)

(Peter & Cerny, 2018)

(Cerny et al., 2019)

Laboratory of structural proteins, Head: Zdeněk Lánský, junior laboratory

Cytoskeletal networks form the internal dynamic scaffold of living cells essential for key cellular processes, such as cell division or morphogenesis. Cytoskeletal proteins self-assemble to drive these processes. Our aim is to understand the principles that underpin their collective action resulting in the coherent behavior of the cytoskeletal networks. We reconstitute cytoskeletal networks from individual components *in vitro*. Using genetic manipulations, biophysical methods with single molecule resolution, and mathematical modelling, we quantitatively explain the studied systems.

(Ludecke et al., 2018)

(Siahaan et al., 2019)

(Schmidt-Cernohorska et al., 2019)

3. Cooperation within international research area

In the institute, we recognize cooperation at local, national, and international levels as a crucial component of excellent research. By collaborating with scientists at the top of their fields in national as well as international institutions, we strive to realize the full potential of IBT researchers. The need to guide IBT in the direction of international excellence-initiated formation of an international Scientific Advisory Board, which was approved in March 2020 and established in May 2020. We expect that the SAB will provide input regarding significant decisions about the future research direction.

Our collaborations can be divided into several areas as listed below.

Students. We recognize international talent and feel competent to attract PhD students from abroad to work at our institute. In years 2015-2019 we employed 36 foreign PhD students from 10 countries.

Our international cooperation is also focused on exchanges of our PhD students and young researchers. In 2018 and 2019 they realized 6 month research stays at Weizmann Institute of Science, Israel; University of Iowa, USA; Malaghan Institute of Medical Research, Wellington, New Zealand; University of Barcelona, Spain; Martin-Luther University Halle – Wittenberg, Germany.

International infrastructure. IBT´s core facility Centre of Molecular Structure (CMS) belongs to the Czech Infrastructure for Integrative Structural Biology (CIISB), together with partner laboratories of CEITEC, Masaryk University in Brno (https://www.ciisb.org/). In 2017 the infrastructure received a Czech Infrastructure for Integrative Structural Biology for Human Health project funded from the European Regional Development Fund. The project´s duration is 48 months with a total allocation of approximately 10.5 million EUR. From 2016 the infrastructure has been also receiving operational funding from the Czech Ministry of Education, Youth and Sports ranging from 1.4 to 1.5 million EUR per year. This collaboration allows us to provide state-of-the-art services for national and international scientists.

CIISB is part of Instruct-ERIC, a Pan-European distributed research infrastructure making high-end technologies and methods in structural biology available to users. We are one of 13 member countries providing open access to cutting edge structural biology, specifically supporting research that uses integrated approaches and technologies. Thanks to this collaboration, we have realized two international training workshops (2018, 2019).

In collaboration with the Laboratory of dr. Vaněk, Charles University, we have contributed to the realization of the events of the ARBRE-MOBIEU – a research network focused on development and application of biophysical methods in molecular and cellular biology (Cost Action, Lead partner, Institut Pasteur, Paris). This collaboration enabled our successful application to the newly emerging European consortium of facilities providing access to biophysical methods. In May 2020 we applied to the EC INFRAIA call as a part of the consortium.

Our expertise in structural bioinformatics prompted us to initiate one of the ELIXIR communities called 3D-Bioinfo in the fall of year 2017. 3D-Bioinfo was forming during 2018 and was finally recognized by the ELIXIR leadership in the spring of 2019. The White paper of 3D-Bioinfo was published in March 2020 (https://doi.org/10.12688/f1000research.20559.1).

International grants. We strive to receive grants supporting international collaborations. A collaboration with the laboratory of Biomedical Research Centre in Giessen, Germany is currently supported by a joint bilateral grant funded by the Czech Science Foundation and Deutsche Forschungsgemeinschaft. A close collaboration is established with the Centre of Biosciences of the Slovak Academy of Sciences and supported by bilateral grants between the Czech and Slovak Academies of Sciences. The cooperation between Taipei Medical University and IBT was approved in 2019 to support an exchange program that will primarily be used by the group of Reproductive Biology.

Examples of international collaboration of individual laboratories and research groups. International cooperation is one of the key factors of research of all our groups and is promoted at all levels in IBT. Our groups participate in joint projects, bilateral agreements, or simply in solving particular scientific

problems. Our scientists are regularly asked by foreign institutes and universities to give lectures as invited speakers, or collaborate on research projects (USA: Carnegie Institution for Science, Stanford, CA; UC Davis, CA; Rutgers University, NJ; Johns Hopkins Drug Discovery, Johns Hopkins School of Medicine, Baltimore, MD; Washington State University, Pullman, WA; University of Iowa; Germany: University of Lubeck; University of Heidelberg; TU Dresden; MPI-CBG, Dresden; Technische Universität München, Charles-Tanford-Proteinzentrum, Martin-Luther-Universität Halle-Wittenberg, Halle; Italy: University of Padova; France: Institute Pasteur, Paris; University of Paris Sud; Genome Engineering Facility Institut Curie, Paris; Institut de Biologie Structurale, Grenoble; Australia: Monash University and University of Queensland, Melbourne; University of Western Australia, Perth; University of Sydney; Denmark: University of Southern Denmark; University of Copenhagen; Sweden: Karolinska Institutet, Stockholm; Upsalla University; Slovenia: Jozef Stefan Institute, Ljubljana; South Korea: Seoul National University; Taiwan: Taibei Medical University; Taiwan National University, Taibei; New Zealand: Malaghan Institute, Wellington; Otago University, Christchurch; Hungary: Institute of Enzymology, Budapest; Slovakia: Commenius University, Bratislava; Switzerland: University of Geneva; The Netherlands: AMOLF, Amsterdam; Israel: Weizmann Institute of Science, Rehovot). A few of our scientists have dual affiliations with foreign universities, which provide a unique opportunity for long-term, in depth projects linking the Czech and foreign laboratories. The outcomes of international collaborations lead to many published papers.

National cooperation is realized on two different levels, one being research collaborations (grant applications and publishing activities) and the other teaching and mentoring future scientists.

Teaching. The extent of our teaching activities is described in detail in section Cooperation with universities. The number of courses and supervisions shows we take the role of educating up-and-coming scientists seriously and see it as an opportunity to establish relations with potential future colleagues. The list of universities we cooperate with in our teaching activities include the highest ranked universities in the Czech Republic: Czech Technical University in Prague; University of Chemistry and Technology, Prague; Charles University, Prague; South Bohemian University České Budějovice.

Research collaborations. Our national research collaborations are numerous and are realized especially with other institutes of the Czech Academy of Sciences and the leading universities. In 2016 the Institute of Biotechnology moved its seat and all laboratories to the BIOCEV center funded by the European Regional Development Fund. It is a joint project of six institutes of the Academy of Sciences of the Czech Republic (Institute of Molecular Genetics, Institute of Biotechnology, Institute of Microbiology, Institute of Physiology, Institute of Experimental Medicine, and Institute of Macromolecular Chemistry) and two Prague faculties of the Charles University (Faculty of Science and First Faculty of Medicine). The project's goal was to establish a European Centre of Excellence in biomedicine and biotechnology. The Institute of Biotechnology is a key part of the center, participating in two research programs, Structural Biology and Protein Engineering (head of the program is B. Schneider from Team 2) and Development of Diagnostic and Therapeutic Procedures.

In 2016 we have successfully commenced a collaboration with the Institute of Physics of the Czech Academy of Sciences when we received a Structural dynamics of biomolecular systems project ELIBIO funded from the European Regional Development Fund. The project´s duration is 71 months with a total allocation of 245 million CZK.

4. HR policy of the institute

IBT has a good age and education distribution of employees. The age structure of IBT is detailed in section 5 below, here we summarize: by the end of 2019, 70 out of the total 144 scientific staff were under 30 years of age. This category covers students of bachelor, master but mostly doctoral studies, who are the future of the institute. The middle category between 30 to 50 years consisted of 61 employees, mainly post-doctoral students and researchers, who are engaged in projects and supervise students. 13 employees were over 50 years old and mostly represent experienced researchers who mentor students and give lectures at universities; some are part of the administration of IBT.

As a part of the center BIOCEV, IBT is located just outside Prague, and needs to be able to offer attractive conditions to all its employees but mostly to students. Senior researchers of IBT therefore liaise with universities in the capital city and other major cities of the Czech Republic for example by giving lectures to attract young talents to our laboratories. All PhD and most Master and Bachelor degree students are employed by IBT giving them a level of financial support. As a result, all laboratories are quite successful in obtaining doctoral students, graduates, and students of European Erasmus projects. This is essential for the fulfillment of their research tasks. At the same time, IBT fulfills an important function as a training workplace for the future educated and confident generation. The lab leaders as well as IBT management support the current good cooperation with universities, especially with partner faculties from the Charles University, but also with faculties at the University of Chemistry and Technology, Prague, the University of Chemistry and Technology in Prague, and the University of South Bohemia in České Budějovice. We have started to coordinate the admission procedure of PhD students at several biomedical institutes from the bio-medical campus and BIOCEV according to the model introduced by the Institute of Molecular Genetics. The importance of IBT as a training workplace is underlined by the pedagogical activity of several of its employees at universities.

When looking for new employees, we cannot limit ourselves to the Czech Republic. Especially in situations where the number of potential PhD students is declining, it is necessary to attract students, postdocs, but also senior workers outside the Czech Republic. Despite a still tangible gradient between the “western” and Czech salary levels we managed to hire senior postdocs from Spain, Germany, or Greece. By the end of 2019, there were 42 PhD students employed at IBT, 17 from the Czech Republic, 9 from Slovakia, 5 from India, 2 from Germany, 2 from Serbia, 2 from Ukraine, 1 from Grenada, 1 from the Netherlands, 1 from Portugal, 1 from Russia, 1 from Vietnam.

Supervision of undergraduate and graduate students is distributed among researchers of the team according to their specialization and training capabilities. Both students and researchers are encouraged to apply for national and international funding, participate in advanced training activities on national or international level, and present their results regularly in international events, conferences, workshops, and the like. The individual laboratories hold weekly and monthly meetings, biannually the institute organizes a two-day conference. These formal events present opportunities to discuss current results, network and solve organization issues. The atmosphere in IBT encourages all employees to discuss any scientific, social, and personal issues openly. The positive impact of our HR policy is reflected in our scientific results and in the high level of competitiveness of our alumni in applying for their next position. Several of our former PhD students are now successful post-doctoral fellows in prestigious institutions in Sweden, United Kingdom, Belgium, Israel, France.

International cooperation of our Institute enables us to send our young researchers and PhD students abroad on various mobility projects. In the years 2018 and 2019 alone, we have sent 5 employees to 6-month internships to USA, Israel, Spain, Germany, New Zealand. For the years 2020-2022 we have planned 13 international internships to Germany, Sweden, UK, Netherlands, USA, Canada, Israel, and France.

The senior members of the laboratories are encouraged to obtain the pedagogical title Assistant Professor (docent) and Professor because, especially for younger colleagues, working at universities helps to promote their further careers. In the future, we plan to motivate the employees to seek formal ways of acknowledgement of their academic careers even more and will motivate them to obtain academic titles Doctor of Science (DSc), Assistant Professor (docent), and Professor.

The HR policy of our institute is based on open position calls and the selection of most qualified candidates in an unbiassed and fair selection process, resulting in recruitment of talented researchers and students on all levels. The recruitment process is detailed in Act No. 283/1992 Coll. and in the Statutes of the Czech Academy of Sciences. New employees are recruited by interviews, and the list of required qualifications is published on the websites of IBT, BIOCEV, Academy of Sciences, and commercial advertisers. The Heads of Laboratories are also recruited via common media, with requirements published a minimum of three weeks before the application deadline. The selection of the employees is done by a three-member committee appointed by the Director and documented in the minutes of the interviews. The onboarding process of new employees is standardized by internal guidelines and among others includes work safety and fire safety courses and tests.

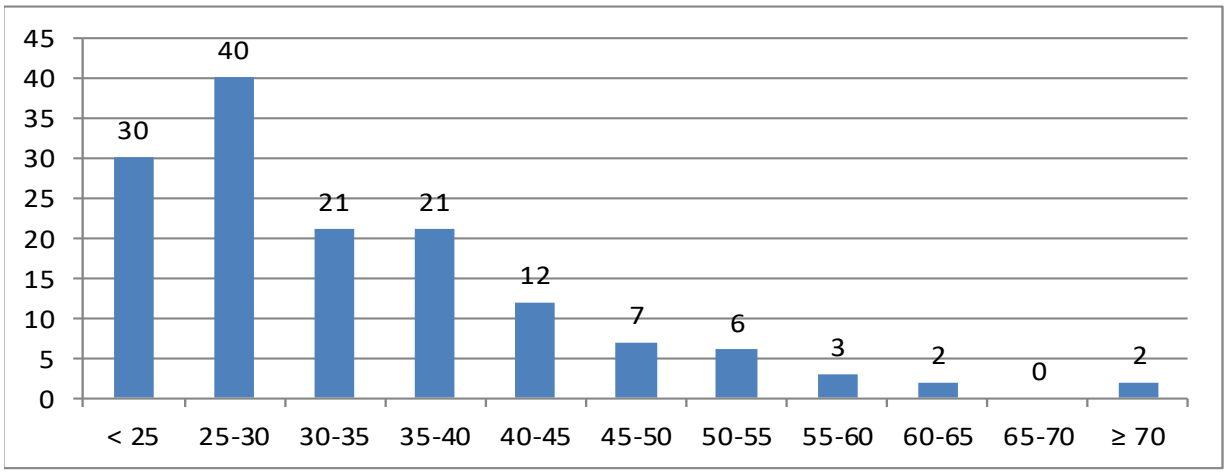
As a part of BIOCEV, IBT adheres to the gender policies and policies for the age structure of the center. We commit to not discriminate job applicants based on their gender, marital status, age, or any characteristics from the anti-discrimination law.

Researchers are regularly (every three years) attested according to the complex requirements specified and approved by the IBT Board. The goal of attestations is to enhance research activities of the institute, motivate researchers to professional growth, and provide researchers the opportunity for structured self-reflection. The Attestation Committee consists of three internal and two external members. The Committee assesses publication activity, filing patents, pedagogical activity, grants, industry collaborations, and other professional engagements such as activities at other institutes, scientific boards, editorial boards of journals, workshop organization etc. Laboratory Heads can ask for an increase or decrease of the qualification category at the time of attestation or in the meantime.

Based on the internal order of the Director No. 3/2018, our Institute has guidelines for taking care of its employees regarding their qualification improvement and work-life balance. For example, employees may receive paid time off for the purpose of qualification improvement, they may receive unpaid time off if requested, or employees with handicaps and parents caring for an underaged child may request special help and working conditions.

5. Age structure of the institute related to December 31 2019

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	30	40	21	21	12	7	6	3	2	0	2



6. Strengths and weaknesses of the institute

In this chapter, we summarize our view of IBT's potential and what can endanger its realization. We restrain from most details in this outline, they can be found in other chapters of the evaluation.

Strengths

- High quality, well focused research program of all laboratories
  - Witnessed by the published papers and application outputs
- Projects with application potential
- Highly qualified and loyal employees
  - A broad spectrum of expertise from physics to medicine
  - The senior scientists are qualified to mentor new generations of scientists
- Good age structure of the research staff
  A large number of students
- Friendly and good-natured atmosphere
- Functioning and well-equipped infrastructure and service laboratories
- Above standard and in several aspects top of the line equipment
  - Owned by both IBT and other BIOCEV partners
- A well-established network of collaborating laboratories nationally and internationally
- Excellent project (grant) financing
  All of our laboratories are well funded, the sufficient level of financial support has been maintained over time

Opportunities

- Synergies resulting from deeper cooperation between both research directions
- Mature research projects leading to great scientific and application outcomes
- Voluntary and logical merging of topics of individual laboratories will prevent fragmentation of research and lead to outcomes of higher impact
- To transform the current SARS-CoV-2 crisis into strengthening IBT´s position as a center of biomedical research able to solve serious socioeconomic threats

Weaknesses

- Laboratories work on many relatively small projects
  - This fact is mostly a consequence of the currently existing short-term grant system
- Limited cooperation with industry
  - We need to extend our contacts beyond the limited Czech biotech and pharma industry
- Still a limited acquaintance abroad.
  We must systematically work on branding IBT, BIOCEV and the Czech Academy of Sciences
- The location of IBT outside of Prague
  - It can potentially lead to issues to attract students and the best scientists who would prefer to work in the metropolis. Fortunately, not a realized threat but we have to be aware of it.
- Potentially, complacency with current achievements

Future Threats

- Reduction of institutional funding
- Reduction of project financing
    - Both above threats became more imminent with the seriousness of the economic decline caused by the Coronavirus pandemic
    - We have to diversify from mostly national grant resources and also apply for more substantial and long-term funding, for example from the EU structures and other international providers
- Possible organizational, financial, and conceptual problems associated with the restructuring of the BIOCEV center at the end of the period of its formal sustainability (end of 2020)
- Ever growing administrative duties will break the sustainable level
    - This applies mostly to the PIs and senior researchers whose time to mentor students and perform the actual research is shrinking
- Incorrectly chosen direction of technology development, which would limit the possibilities to follow new research trends
- Termination of external financing of large infrastructures, currently cutting-edge instruments will become obsolete
    - The Center of Molecular Structure managed by IBT is a part of a Pan-European infrastructure. CMS operations need to be continuously supported and its equipment must be kept at the highest technological level to be competitive. The same applies for two BIOCEV infrastructures, the optical facility and the Czech Center of Phenogenomics, both critical for science outcomes of IBT
- Failure to attract students
- Employment of students will not be possible because of tendency of universities to isolate themselves or poorly set conditions for PhD studies

7. Assessment of the strategy plan of the institute for the period of 2015-2019

During the evaluation period 2015-2019, IBT has become a well-established member of the Czech national and international research community. The previous evaluation period (2010-2014) could be characterized as the time of team establishment; our major tasks within that period were to develop, stabilize, and sustain our research activities. The goal has been to design and build a strong, internationally recognized research group with synergy between individual Research Laboratories. The plan for the years 2015-2019 was to further build on these foundations, expand the achieved expertise, mastered methods and techniques, consolidate the team and research infrastructure. During this period, our plan was to reach the critical mass of human potential and technical means to conceive and perform large and ambitious projects of scientific excellence, further strengthening our collaborations and involvement in the international community. As evidenced in detail in the chapters above, we have succeeded in implementing all of these planned features. IBT personnel as well as the institute research infrastructure is consolidated, which enabled us to generate multiple exciting results over the evaluated period of 2015-2019.

To highlight a few important points, IBT and its employees have:

- worked in accord with the plans outlined in the previous Evaluation report;
- increased the scientific output and its scientific excellence;
- increased its application output;
- successfully concluded planning and building of the center BIOCEV and became one of its most active participants;
- been actively involved in the activities of the Czech Academy of Sciences under the umbrella of Strategy AV21;
- participated in teaching semestral courses as well as mentoring students;

- participated in popularization and PR activities.

As a result, IBT is now well established within the international scientific community leading to its higher international visibility.

8. Implementation of recommendations from past evaluation (*)

The international committee pointed out very few areas for improvement in the year 2015, its assessment of IBT activities in the period 2010-2014 was very positive. Below we answer three suggestions from year 2015.

- Focus the research on a smaller number of topics. … This may be of even more importance after the institute moves to the BIOCEV location, requiring possibly additional coordination of work with other teams.

The scope of research of IBT laboratories is a topic we are very aware of. It is related to relatively small (in financial terms) and short term (typically three-year) grant projects. All lab leaders and many senior scientists have to answer various grant calls, often with contradictory conditions: only basic research in the Czech Science Foundation (GA ČR) vs. the necessity to produce applied results without impacted publications in the Technology Agency of the Czech Republic (TA ČR) or the Czech Health Research Council (AZV ČR). Even when IBT achieves significantly above-the-average success rate in obtaining grant projects, the system leads to fragmentation of the research topics.

We are aware of the problems and systematically look for longer term projects and projects supporting more people. The portfolio of research topics is also kept under control by encouraging collaboration between laboratories and by finding the common methodological grounds to be able to share the technical expertise and save the human resources.

A more detailed answer to the recommendation is under the text of Team 1.

- The elaboration and execution of joint projects with ELI should be encouraged and supported.

The joint project with ELI was executed and led to the establishment of a new research direction in the area of structural biology.

The infrastructure-oriented activities have been broadened to application to the newly arising consortium of facilities providing access to biophysical techniques. The application was evaluated and the Centre of Molecular Structure was accepted as a unit of the new consortium called MOSBRI competing now for support in the INFRAIA call of the European Commission for support of starting infrastructures.

- Continue in the planned activities to achieve higher publication activities.

For any basic science research institution, this is a fundamental imperative. As we present above, the number and impact of our publications (as measured by the average impact factor) has been increasing during the last five years.

(*) *We assume that the current evaluation commission has available the full text of recommendations of the previous evaluation commission and we do not cite it here.*

9. Strategy plan of the institute as a whole for the period of 2020–2024

Continuation in the established trends. The future research of IBT will organically grow from the ongoing projects. The most promising projects will be further supported with the goal to enforce our research excellence. It is essential to maintain the current character of IBT as an institution concentrating on basic research. Below we discuss the ways how we intend to steer the institute in several key areas.

Highly qualified, loyal employees and students. We want to keep the balance between experienced senior scientists and young enthusiastic postdocs and students. New employees will be selected based on widely advertised interviews open to applicants from around the world. Especially in situations where the number of students is declining, it is necessary to look for PhD students, postdocs, and senior workers outside the Czech Republic. We have joined an admission procedure of PhD students already established at several biomedical institutes from the biomedical campus Krč, according to the model introduced at the Institute of Molecular Genetics of the Czech Academy of Sciences. However, it is realistic to expect that their majority will be recruited from the Czech Republic. To be able to attract a sufficient number of PhD students, we need to support the current good ties with universities, especially with partner faculties of Charles University, the First Faculty of Medicine and the Faculty of Science, but also with faculties at the University of Chemistry and Technology, Czech Technical University, and South Bohemian University in České Budějovice. We will continue with our teaching and other pedagogical activities. In this context, especially young IBT researchers will be encouraged to get involved in teaching semestral courses because affiliation with universities is important regarding their future careers.

Collaborations as a modus operandi of our work. As in its history, IBT must actively seek effective scientific cooperations in the Czech Republic and abroad. Our main partners remain our colleagues from the BIOCEV center and the Czech Academy of Sciences. Our participation in the BIOCEV project is advantageous since it has reached a good reputation, also due to IBT´s scientific results. The center has a number of employees sufficient to overcome the critical mass of people in several critical areas of expertise such as structural biology, microscopy, or development and maintenance of animal models. The resulting wide range of methods available at BIOCEV allows for synergies between different research approaches. The IBT staff has excellent equipment at its disposal, whether it is owned by IBT, partner institutes of the Academy of Sciences, or by either of the partner faculties of Charles University.

At the end of year 2020, the period of sustainability of the project ends. We are actively negotiating the future arrangement in the center with the aim to strengthen IBT´s position. Undoubtedly, the critical step is transferring the share of the ownership of the BIOCEV main building and related equipment of the Institute of Molecular Genetics into the hands of IBT.

Stabilization or growth? The current size of IBT with eleven laboratories and about 150 employees is functional and contributes to a good performance. Any future expansion will be carefully examined and executed only in case a proposed enlargement opens up a new promising direction of research. As is mentioned above, the sustainability of the BIOCEV project ends at the end of 2020. It may or may not open ways of IBT´s expansion, either by an inclusion of a few laboratories of the BIOCEV partners or by gaining more space. In either case, IBT´s growth will be thoroughly scrutinized and accepted only if deemed advantageous.

Importance of availability of top techniques. The three infrastructural (service) laboratories are and will remain an integral and significant part of the IBT organism. All three, the Center of Molecular Structure (CMS), Gene Core - Quantitative and Digital PCR and the Service Technology Laboratory, are discussed elsewhere, in some detail in chapter 16 below.

Funding. IBT is well above the standard success rate in obtaining grant projects and we will strive to be as successful as up until now. In this context, it is useful to stress the importance of work of IBT scientists in grant agencies, ministerial commissions, and other bodies that decide on the financing of science. Our broader participation will be encouraged.

Status of the institute. IBT is and will remain an integral part of the Czech Academy of Sciences. We

will keep close ties with the institutes in the biomedical campus Krč. Our standing in the BIOCEV center and its importance for the institute has already been discussed. It will be essential for the future of IBT that the current moral and financial support by the Academy of Sciences, primarily by its executive body, the Council, but also by the management of other institutes, will remain.

We will seek closer collaboration with one of the Academy´s institutes, the Institute of Organic Chemistry and Biochemistry, IOCB. IOCB has a history of extremely successful transfer of results of basic research into the pharmaceutical industry and has the know-how of knowledge transfer and the means to execute it. Both institutes have complementary strengths and we will coordinate their combination with the goal to learn and realize some of our potentials. Especially IBT´s Team 2 closely collaborates with the center CEITEC, a structure biology unit at Masaryk University, via our involvement in the Czech infrastructure of Instruct-ERIC.

Transfer of knowledge, application potential. Our potential transfer and application activities will remain to be based on our basic research. Transfer of knowledge is already a part of the workflow in most laboratories, a few examples are mentioned in the following chapter, but projects with a potential for being applied (in a broad sense) need to be identified more systematically than they currently are. In this sense, we believe that the political and societal pressure to transfer scientific results to the application sphere and turn basic science into tangible results will grow. We are getting ready to positively answer the growing pressure. Transfer of knowledge will be supported systemically in IBT by strengthening the role of our Technology Transfer Officer and by linking his/her activities to the Public Relations, and project (grant) management workers.

A great success of prof. Neužil and his team, who managed to transfer their basic research to the phase I clinical study, shows that even in a relatively small institute and with limited resources, significant results can be achieved. We will work toward identification of projects with application potential and support them within IBT, search for their support by the Academy of Sciences, IOCB, and by private entities. The slowly improving atmosphere in relation to research will hopefully bring new opportunities in finding the venture capital for the emerging projects.

The current turbulent situation connected to the SARS-CoV-2 pandemic has put new limits to our work, but we believe it has opened up even more opportunities. BIOCEV showed its strength and real synergy in establishing cooperation between both Faculties of Charles University and IBT. We combined our expertise in virology and advanced analytics of biological samples and organized a team testing for SARS-CoV-2. The team was established in mere days as a reaction to the urgent demand and worked in shifts to analyze thousands of medical samples. We intend to work on the established ties and propose the formation of a formal and permanent task force able to respond to future health risks.

10. Research for practice

10.1. Principles of knowledge transfer in IBT

The institute concentrates on curiosity driven research, but we are aware of our social responsibility so that transferring research results into practice is an integral part of our research work. IBT has a clearly defined pipeline that regulates the process of transfer of knowledge including rules for IP protection In collaboration with individual researchers, the technology transfer officer monitors the results of individual laboratories in terms of their potential use in practice and negotiates with the laboratory heads and the IBT management further steps, typically patent pending or selling of products or know how. Transfer of knowledge in IBT includes cooperation with suitable partner institutions, companies or investors, offering a license, selling an IP or transferring it to a spin-off. We strive to establish cooperation with foreign institutions, companies, and investors, which would increase the quality and attractiveness of the result in terms of its transfer into practice.

10.2. Examples of successful transfers

During the evaluation period 2015-2019, IBT filed eight patents listed in table below.

Title (Laboratory Head)	Application	State		Remark
Trifenylfosfoniové analogy biguanidu Triphenylphosphonium biguanide analogs, the method of their preparation and their use as a medication (Neužil)	PV 2015-227		granted CZ307146	Czech application (international application abandoned)
Deferoxamine derivatives as medicaments (Truksa)	PCT/CZ2018/050036	in process		international application
PSMA-specific binding proteins (Bařinka)	PCT/EP2016/065993	European in process	granted US10406247	international application
Polypeptides for the treatment of autoimmune diseases based on blocking the p19 subunit of the IL-23 human cytokine (Malý)	PV 2016-329		granted CZ307849	Czech application
Development of new monoclonal antibodies recognizing human prostate-specific membrane antigen (PSMA) (Bařinka)	PCT/US2018/012530	in process		international application
Compounds for treatment of senescence-related disorders (Neužil)	PCT/EP2017/079362	in process		international application
3,5-bis(phenyl)-1H-heteroaryl derivatives as medicaments (MitoDFX) (Truksa)	EP19180438	in process		European application, may continue as international
Polypeptides mimicking epitope of VRC01 broadly neutralizing antibody as antigens for development of a vaccine against HIV-1 infection (Malý)	PV 2019-585	in process		Czech application, may continue as international

Neuzil laboratory. The project of mitochondrially targeted cancerostatic compound MitoTam, described in the evaluation text of Team 1 (Part 3.4), demonstrates the power of basic research in finding applications of the greatest potential. The agent has been also found to act as a senolytic compound, i.e. selectively killing malignant as well as non-malignant senescent cells.

(i) We have been collaborating with Czech investors SmartBrain s.r.o. and KKCG a.s. to run a clinical trial phase 1/1b in the General University Hospital in Prague. At present, we are finalizing Phase 1b (long-term toxicity) study, with very promising results. We are planning Phase 2 study to be launched later in 2021.

(ii) Based on senolytic activity of MitoTam supporting by unexpectedly positive effect in obesity-linked type 2 diabetes mellitus, we are planning a clinical trial together with our collaborators from the Diabetology Centre of the Institute of Clinical and Experimental Medicine in Prague. We are currently looking for an investor and anticipate to start the trial second half of 2021. A positive point in favor of this study is that we will use a similar regimen as during the oncology Phase 1 and 2 study. Of pathologies that are typified by high number of prematurely senescent cells, MitoTam has shown particularly efficient against type 2 diabetes mellitus (T2DM) in a mouse model of obesity-linked T2DM, lowering the body weight and normalizing markers of the pathology. We plan a clinical trial, since 35-40% of population of >45 years of age are suffering from T2DM. Since obesity-linked T2DM is the most complicating co-morbidity of the Covid-19 disease, we propose that MitoTam may alleviate the severity of the pathology.

Barinka laboratory has a strong long-term interest in prostate-specific membrane antigen (PSMA), an established biomarker for the imaging and experimental therapy of prostate cancer (over 30 manuscripts, 70 crystal structures). Based on our basic research achievements regarding PSMA, we have been approached by:

(i) Company Piere-Fabre – we provided consultancy, contract inhibitor testing, and on-demand protein production (2015 – 2016). This contract was worth more than 20 kEUR.

(ii) Company Bayer – on-demand protein production, crystallization grade; (2017), 10 kEUR.

(ii) We developed and humanized anti-PSMA monoclonal antibodies. Patents negotiating licensing is going on with several companies, including the Czech company Sotio.

(iv) We sold mAbs to several entities (research institutes, hybridoma to companies – e.g. Abcam.

(v) Another major focus of basic research of Barinka laboratory, 11 zinc-dependent HDAC, succeeded in preparing all 11 zinc-dependent HDACs, and established their *in vitro*, cell-based assay, crystallography and ADMET platforms. This led to:

(vi) Collaboration with Starwise Inc, NHF Pharma – contract research, profiling of isoform selectivity of inhibitors, structure-assisted drug design. Agreement leads to monetary as well as research (manuscripts) benefits.

(vii) Development of anti-HDAC6 specific mAbs that are being offered by Merck catalogue.

(viii) Sold purified HDACs anti-HDAC6 and mAbs to companies (e.g. Merck), licensed hybridomas (EXBIO).

Barinka lab has established a versatile expression platform for heterologous expression of recombinant protein production (from *E. coli* to HEK293) and the know-how enabled realization of two projects supported by Central Bohemia Innovation Vouchers (approximately 200 kKc each) with the Czech company Apronex.

Kubista laboratory of Gene Expression has developed two-tailed technology for microRNA analysis (Androvic et al., 2017) (Androvic et al., 2019). It has been developed in collaboration with a small company TATAA Biocenter and has been recently licensed by Czech biotechnology company BioVendor. The highly specific and sensitive Two-Tailed PCR technology provides BioVendor with rock-solid base to establish own diagnostic miRNA panels, broaden the life science portfolio, and kick-start BioVendor's rapid expansion in the miRNA market. New applications of Two-tailed technology are currently discussed with other companies in the market (e.g. MultiplexDX™ International).

Truksa laboratory of tumor resistance has developed a novel class of iron chelators which are targeted to mitochondria in cooperation with Service technology laboratory. These compounds show promising anti-tumor and migrastatic properties in mice models and thus have considerable translational potential. This has resulted in several patent applications with Smart Brain as a co-applicant (deferoxamine derivatives as medicaments WO2019015701A1, US2020078379A1; (3,5-bis(phenyl)-1H-heteroaryl derivatives as medicaments EP19180438.4).

Komrskova laboratory of Reproductive biology has developed new innovative technologies the to be used as reliable and quick diagnostic tool for sperm quality assessment and also for selection and separation of healthy sperm for further used in assisted reproductive techniques in human and veterinary practice (Intellectual property rights: EP20152484.0; EP20152470.9; PV 2020-224; PV 2020-223). This novel technology is based on protein CD46, which is part of the sperm head (particularly acrosome), but it is not surface exposed in healthy sperm and it is detectable only if sperm head is damaged. Moreover, it uses the knowledge that when sperm acrosome is damaged there is consequential damage of DNA due to increased oxidative stress and also there is decreased sperm motility.

Based on the ongoing successful collaboration between three subjects such as the biotechnological company PrimeCell Bioscience, a.s.; Faculty of Medicine, Masaryk University and University Hospital Brno we aim to fill the gap between identification of a novel target and evaluation of the interventions' efficacy within a studied field or the intended clinical use in population. Base on the collaboration with Czech University of Life Science, Prague, we also address used of the novel sperm selection technology in veterinary practice. Based on preliminary testing and obtained results the novel technology for human and veterinary sperm quality assessment has great potential to become a new widely used method allowing to improve sperm diagnostic as well as selection of sperm to be further used for fertilization of human oocytes or oocytes in specific animal breeding programmes

such as horses, cattle or domestic and endangered animals.

Dohnalek laboratory of structure and function of biomolecules has a well-established and long-term collaboration with Novozymes A/S. It has led to explanation of behavior of the active site of enzyme bilirubin oxidase, crucial for several medical and biotechnological applications, including determination of blood level of bilirubin and development of nanotechnologies and bio-fuel cells. Our results show that substrate selectivity of the enzyme can be influenced and external conditions are crucial for a given application. The collaboration attracted ~ 20,000 EUR for IBT in the relevant period.

The infrastructural Center of Molecular Structure has regular commercial users of research services, including BioVendor; Dekonta a. s.; Contipro a. s.; Affipro s. r. o.; Alfarma s. r. o., Novozymes, annually worth approximately 8 kEUR.

CMS has signed a contract with company Anton Paar to develop SAXS technologies on the platform SAXSPoint 2.0, about 6 kEUR.

An ability to answer to the socio-economic needs is our response to the Coronavirus crisis. In collaboration with our BIOCEV colleagues from Charles University, we established a pipeline of PCR-based testing of Corona virus in human samples. In addition, over 20 IBT employees, technicians as well as scientists joined the team to isolate RNA and analyze its presence by qPCR. Method of RNA quantification by qPCR method of the virus was significantly modified and optimized by the IBT team and it contributed to the success of the testing site.

11. Strategy AV21

The strategy of the Czech Academy of Sciences responds to current social challenges through a sophisticated formulation of eighteen research programs, based on cooperation of scientific fields and institutions. The basic program framework of the Strategy AV21 was accepted by the Academy Assembly in 2014. The research programs of the Czech Academy of Sciences are open to partners from universities, corporations, and institutions of regional administration, as well as foreign research groups and organizations.

The Institute is involved in two programs of the Strategy AV 21:

11.1. Research Program 7: Wellbeing in Health and Disease

The main goal of the program is to develop more effective strategies to prevent and treat lifestyle-choice related diseases. The program aims to directly develop innovative diagnostic tools and therapies to prevent and treat diseases of modern civilization, minimize their consequences, and promote faster recovery. The program also supports meetings of scientists and students.

IBT is involved in the sub-program “Early diagnosis and treatment of patients - the path to human health”. The goals of the program are fulfilled by the implementation of events organized by IBT: “Symposium of Immunology and Biology of Reproduction” and “Discussion on Structural Molecular Biology”.

The traditional symposium, “Biology and Immunology of Reproduction”, brings together scientists from reproductive biology and physicians from the field of reproduction in human medicine. Both parties receive information on reproductive research at the molecular level and on patients' reproductive problems. Symposia are held regularly every year in May in Liblice with the participation of approximately 50 participants, including students. The “Discussions in Structural Molecular Biology” is a representative and traditional nationwide presentation of the results of structural biology research in the Czech Republic and, to a large extent, in Slovakia. Conferences are regularly held in March in the Nové Hrady Conference Center with the participation of 120 - 130 scientists and students.

11.2. Research Program 18: Preclinical testing of potential pharmaceutical

The goals of this program are coordination and development of potential pharmaceuticals and their

comprehensive preclinical testing at CAS institutes, synergy enhancement in the utilization of resources for basic and applied research, reducing the cost of research into pharmaceuticals, fostering collaboration between the academic sector and commercial entities, etc.

IBT fulfills the goals of the second program through activities of the Service Technology Laboratory (STL). STL is a core facility focused mainly on medicinal chemistry, preclinical development, and advanced technology transfer. STL is a member of the AV21-CAS strategy for preclinical evaluation of potential new drugs that identifies molecules suitable for further development in medical applications. STL designs and synthesizes new potentially biologically active substances which are used by our collaborators for basic or applied research. STL is also involved in *in vitro* screening of newly prepared substances and evaluation of Structure Activity Relationship (SAR); basic toxicological assessments such as Maximum Tolerated Dose studies (MTD), or pharmacokinetic studies (FK). Pilot pharmacodynamics studies for oncological indications is another segment of activities. STL is also involved in medicinal chemistry activities beyond the usual academic scope, mainly relevant to advanced drug development. When needed STL synthesizes substances, impurities, and metabolites in certified quality suitable for advanced preclinical evaluation under the GLP system. We have experience with a process scale-up as well as with a process transfer for GMP manufacturing.

12. Cooperation with regions of the Czech Republic

As already stated, we believe that cooperation benefits the research progress and helps find the best ways to realize our application potential. IBT is situated just outside of Prague in the Central Bohemian region and within the region, we have a close scientific collaboration with the ELI Beamlines research center (Institute of Physics of the Czech Academy of Sciences). Together with ELI our Institute is solving a Structural dynamics of biomolecular systems project funded by the European Regional Development fund. The project´s running time is scheduled from December 2016 to October 2022 and its allocated funding is 9.4 mil. EUR.

If we stay in the Central Bohemian region, the center BIOCEV is a part of STAR cluster (Science and Technology Advanced Region), a science and technology cluster made up of a strong community of research organizations, companies, investors, and enthusiastic local patriots in the triangle between Dolni Brezany, Vestec and Zlatniky. The region has attracted strong investment from the European funds as well as from private sources and forms an alternative for professional life of young and talented people from a wide region beyond the Czech Republic.

One of our closest collaborations when it comes to regions of the Czech Republic is collaboration with Prague institutions, where a great number of institutes of the Academy of Sciences (Institute of Physics, Institute of Microbiology, Institute of Experimental Medicine, Institute of Molecular Genetics, Institute of Organic Chemistry and Biochemistry) reside as well as several universities (Charles University – First Faculty of Medicine, Faculty of Science; Czech Technical University; University of Chemistry and Technology).

Our Institute, specifically the Centre of Molecular Structure, is a part of the Czech Infrastructure for Integrative Structural Biology, where our partner is the Masaryk University in Brno (South Moravian region). The infrastructure is supported by funding from the European Regional fund as well as the Ministry of Education, Youth and Sports. This collaboration allows scientists from different regions of the Czech Republic and abroad use offered services for financially reasonable pricing.

In South Bohemian´s capital city České Budějovice, we collaborate with the University of South Bohemia in České Budějovice and the Biology Centre of the Czech Academy of Sciences.

13. Cooperation with universities

Overview of semestrial lectures, seminars, and courses

Name of the university	Number of semestrial lectures seminars and courses 2015-2019		
	Bachelor	Master	Doctoral
Charles University	44	45	43
Griffith University, Qld, Australia	10		
CULS, Dpt. Vet Sciences	6	9	
Czech Technical University in Prague	6	15	
University of Chemistry and Technology, Prague		7	
South Bohemian University Ceske Budejovice		5	5

Supervision of students

Type of study	No. of supervised students	No. of consulted students	Theses defended 2015-2019
Bachelor	46	7	34
Master	67	14	41
Doctoral	64	13	22

14. Joint research centers with universities

The institute is an integral part of the research center BIOCEV, a joint research center of the Academy of Sciences and the Charles University in Prague. Research and development performed in BIOCEV is focused on the selected areas of biotechnologies and biomedicine. The scientific scope of BIOCEV has been divided into five research Programs, each of them dealing with a number of separate research projects. Team 1 is responsible for solving Research Program 5 “Development of Diagnostic and Therapeutic Procedures”. Team 2 is responsible for Research Program 3 “Structural Biology and Protein Engineering”. The scientific output and mentoring of students generated within this Program is discussed above in detail.

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

15. Research services

We report both infrastructures as defined by the Ministry of Education and “regular services” under the following chapter *16. Administration of research infrastructures*.

The institute does not offer services of computer databases, biobanks, and does not own physical collections or libraries.

16. Administration of research infrastructures

Research infrastructures are of great importance for the research effectivity of the institute. IBT operates three service laboratories, one of which, the Center of Molecular Structure, is a part of a European infrastructure network Instruct-ERIC. The bioinformatics infrastructure ELIXIR has a strong presence in IBT by our active participation of the ELIXIR community for structural bioinformatics 3D-Bioinfo.

16.1. Center of Molecular Structure, CMS

The Centre of Molecular Structure (CMS) is a service laboratory of the Czech Infrastructure for Integrative Structural Biology, CIISB, a member of Instruct-ERIC (www.ciisb.org, www.instruct-eric.eu/centre/biocev/, www.ibt.cas.cz/core-facility/CMS/). CMS provides state-of-the-art equipment, expertise, and services for characterization of biological molecules and for structural analysis. CMS provides services in an Open Access regime, to internal IBT users and also to any academics or industrial customers. The facilities are operated under the Czech Infrastructure for Integrative Structural Biology (CIISB) and belong to the Czech center of the European structural biology infrastructure Instruct-ERIC. The facility educates Czech and foreign students and young scientists in a number of workshops throughout the year.

The uniqueness of the facility lies in the concentration of top equipment and expertise with a tight connection to IBT research projects and open access approach. Jan Dohnálek (head), Frederic Vellieux (head 2016-2018), research staff: Jiří Pavlíček (*Crystallization of proteins and nucleic acids facility*), Jan Stránský (*Diffraction techniques facility*), Tatsiana Charnavets (*Biophysical techniques*), Petr Pompach (*Structural mass spectrometry*). Technicians: Ľubica Škultétyová, Pavla Vaňková. IT Technician: Michal Strnad.

CIISB is a registered large infrastructure on the Czech Roadmap of Research Infrastructures (https://www.vyzkumne-infrastruktury.cz/en/2019/11/update-of-roadmap-of-large-research-infrastructures-of-the-czech-republic/) and Instruct-ERIC (https://instruct-eric.eu/) is a Pan-European research infrastructure registered on the Roadmap of infrastructures by the European Strategy Forum on Research Infrastructures (https://www.esfri.eu/). The investments into the CMS equipment and operational costs have been in 2015-2019 largely covered by specific projects from MEYS and ERDF for large infrastructures (LM2015043, CIISB4HEALTH no. CZ.02.1.01/0.0/0.0/16_013/0001776, ELIBIO no. CZ.02.1.01/0.0/0.0/15_003/0000447), totaling at 4 979 thousand EUR, with some contribution in the form of access fees.

Biophysical techniques enable assessment of the quality, stability, and interaction properties of hundreds of bio-molecular samples of (not only) demanding structural biology projects, be it regular checks, thorough analysis of properties, or optimization of molecular constructs or handling protocols.

The core facility *Crystallization of proteins and nucleic acids* enables thousands of crystallization experiments using robotic or manual setup, automated monitoring of crystal growth, experiments at selected temperatures or under defined conditions, and preparation of samples for further crystallographic studies.

The Diffraction techniques facility offers crystal quality screening, *in situ* crystal testing, single crystal data collection and processing, small angle X-ray scattering (SAXS) experiments with robotic sample loading and online UV-VIS spectrometry, and SAXS data processing. Hundreds of samples are processed per year in the self-assisted mode or with full staff support.

The core facility *Structural mass spectrometry* provides analyses of hundreds of samples and supports many internal and external structural biology projects. The main focus of the services lies in monitoring of proteins´ structural changes and protein-protein interaction by chemical cross-linking and hydrogen-deuterium exchange. The facility attracts academics and industrial users from abroad.

The key equipment of the CMS enables routine and advanced experiments for internal and external user projects. This instrumentation includes Circular Dichroism (CD) spectropolarimeter Chirascan Plus (Applied Photophysics) enabling comparative structural studies on biological molecules with changing conditions, in mutagenesis, upon ligand binding etc. Vertex 70v Fourier-transform Infrared

(FTIR) Spectrometer enables time resolved infrared spectroscopy providing answers on dynamical processes in enzymes, transcription factors, or structural proteins. Monolith NT.150 microscale thermophoresis is essential for determination intermolecular interaction parameters. Malvern Microcal iTC200 isothermal titration calorimeter enables precise thermodynamic characterization of intermolecular interactions. Robotics for crystallization and crystal growth monitoring – Gryphon (ARI), NT8 (Formulatrix), and the crystallization hotel RI1000 (Formulatrix) provide cutting edge service for protein and nucleic acid crystallization and remote monitoring for structural studies. Single crystal diffractometer D8 Venture (Bruker) with MetalJet D2 X-ray source, large area detector Photon III, automated *in situ* ISX stage and HClab dehydration device enable routine and advanced X-ray diffraction measurements leading to new structural knowledge for the target systems of the team. SAXSpoint 2.0 (Anton Paar) with MetalJet C2+ X-ray source, area detector Eiger 1 M, automated sample loader, *in situ* UV-VIS spectrophotometry, and SEC-SAXS option is a unique in-house device for structural studies of biomolecular systems in solution. Ultra-high resolution mass spectrometer 15T solariX XR (Bruker Daltonics), unique in the Czech Republic, enables advanced mass spectrometry experiments leading to structure-function results on the targets of the team. MALDI-TOF mass spectrometer Autoflex Speed (Bruker Daltonics) enables routine mass spectrometry experiments controlled by users. Excimer laser COMPex (Coherent) is applied in a unique approach of complex formation studies using the fast photochemical oxidation of proteins.

In the evaluated period 2015-2019, the CMS was in service for 4 years (2016-2019), welcomed 431 users performing experiments for 379 projects, of which 117 were external, including users from Austria, Italy, Poland, Tunisia. The CMS services contributed to a significant scientific output of its users, in total in 38 publications in peer reviewed journals, including: Sharma, S., et al., Proc. Natl. Acad.Sci USA (2018) 115(30): E7053-E7062; Rais, R., et al., J. Med. Chem. (2017) 60(18): 7799-7809; Kylarova, S., et al., FEBS J. (2016) 283(20): 3821-3838; Zahradnik, J., et al., FEBS J. (2019) 286(19): 3858-3873; Stafkova, J., et al., Mol. Cell Proteomics (2018) 17(2): 304-320; Zeman, J., et al., Nucleic Acids Res. (2019) 47(15): 8282-8300; Rozbesky, D., et al., Anal. Chem. (2018) 90(2): 1104-1113; Koval'ova, T., et al., Glycobiology (2019) 29(1): 59-73; Koval, T., et al., Scientific Reports (2019) 9: 13; Darebna, P., et al., Clinical Chem. (2018) 64(9): 1319-1326; Trundova, M., et al., Int. J. Biol. Macromol. (2018) 114: 776-787; Podzimek, T., et al., Plant Science (2018) 276: 152-161.

16.2. GeneCore – Quantitative and digital PCR Core Facility

The GeneCore - Quantitative and digital PCR core facility is an academic service provider specialized particularly in high-throughput gene expression analysis using quantitative polymerase chain reaction (qPCR). We have a broad range of experiences that include experimental design, methods for sample extraction, quality control (QC) of nucleic acids, qPCR and digital PCR (dPCR), NGS library preparation (RNA-Seq), and single cell analysis. We also aim to provide the most recent and appropriate methodologies to our customers. Currently, we are proud to be the exclusive provider of a novel method developed by the Laboratory of Gene Expression named Two-tailed RT-qPCR, which allows for the quantification of miRNA. At our facility, academic researchers have the great opportunity to perform their own experiments but under the appropriate supervision.

Our team is composed of four experienced members that have been working for several years in the field of gene expression analysis. We continuously share our accumulated and up-to-date knowledge by providing several training courses that are specialized in QC, qPCR, dPCR, and single cell analysis. These courses have always been well received by our participants, as they provide both essential information on these techniques and also expose the participants to qPCR or dPCR instruments produced by many different manufacturers. If there are any specific requirements from our customer, we can also provide custom-made seminars including a practical part. We also assist with the organization of several conferences which help to enlighten participants with most current developments in the fields. Most recently, our team took part in the organization of an international Single Cell Europe 2018 conference that was held in BIOCEV campus.

Our laboratory is well equipped with several qPCR instruments (BioRad, Roche), including a high-throughput qPCR device from Fluidigm, which allows up to 9216 reactions in only one run. The

equipment for digital PCR is the droplet based system QX200 from BioRad. Robotic pipetting station epMotion P5073 (Eppendorf) and several automatic pipettes (Eppendorf, ThermoFisherScientific, Integra) provide greater efficiency and precision to our routine workflow. Our system used for the single cell collection is the fully automated and flexible microscopic micromanipulator CellCelector (ALS), where each selected cell is transferred to an individual well within a 96-well plate, which could easily be used for any downstream application, e.g. expression profiling.

16.3. The Service Technology Laboratory, STL

The Service Technology Laboratory (STL) is a core facility focused mainly on medicinal chemistry, preclinical development, and advanced technology transfer. STL designs and synthesizes new potentially biologically active substances and is also involved in *in vitro* screening of newly prepared substances and evaluation of Structure Activity Relationship (SAR); basic toxicological assessments such as Maximum Tolerated Dose studies, or pharmacokinetic studies. Furthermore, STL is involved in medicinal chemistry activities relevant to advanced drug development.

16.4. ELIXIR and participation in its community 3D-Bioinfo

IBT scientist have a strong participation in ELIXIR-CZ, a part of the European infrastructural initiative. We have initiated one of the ELIXIR communities, a community on structural bioinformatics 3D-Bioinfo, which embraces excellent European structural bioinformaticians. 3D-Bioinfo is coordinating many bioinformatic activities in Europe such as benchmarking and validation standards. We coordinate the field of the nucleic acid structures.

17. Outreach activities

IBT pays attention to its media image by participating at events organized by the Academy of Sciences, Ministry of Education and other organizations and also by activities of the individual scientists. The latter is summarized sufficiently in the reports of Team 1 and 2, the former can be summarized as follows.

- Yearly in November, Open days of the IBT. Every year 20 to 80 visitors from high schools, individuals.
- A special issue of the Czech edition of the magazine Scientific American, issue 3-4 2019.
- Brochure about IBT activities in the years 2015 – 2019.
- Participation in the project Open Science of the Czech Academy of Sciences in last four years, 8 students from high schools.
- Systematic presentation and popularization of the IBT discovered drug MitoTam in the press, internet, TV.
- Popularization of the IBT input to the research of infertility in various media.
- Popularization of the IBT input to the research of diabetes in various media.
- Collaboration with Weizmann Institute of Science: workshop Frontiers in targeted modulation of protein function with researchers from the Weizmann Institute of Science on November 28-29, 2016. The first part of the specialized workshop was open to the general public.
- Science Festival (Festival vědy), participation by lecturing and installations.
- Week of Science (Týden vědy na Jaderce), presentations and lectures, several years.
- Street Exhibition organized by the Academy of Sciences in 2015.

18. Publishing activity concerning scientific books and periodicals

Combining the total number of published outputs listed in Team 1´s and 2´s part of the evaluation information, the institute published 225 papers in impacted journals, 14 papers in other journals, 6 chapters in scientific books, 46 papers in almanacs, 1 licensed patent, and 29 other applied results.

The book chapters contain both Czech and foreign scientific books: (Fuertes et al., 2019) (Pěknicová, 2016a) (Pěknicová, 2016b) (Sindelka et al., 2017) (Dohnálek, 2016) (Tishchenko, 2019).

As shown in the histogram in chapter 2. Description of the main research directions investigated by the institute of this document, the number of publications published by researchers of the institute has grown over the evaluated period and significantly, the impact of our research has been growing, based on the growing average impact factor of journals we published in.

19. Organized conferences and workshops

As research experts recognized in their respective areas, institute researchers are active in organizing international and national conferences, meetings, and workshops. Details about organized events are presented in the reports of Team 1 and 2, here we only highlight some of the actions.

Neužil J.: Chief Organizer of Annual Conference of the Society for Free Radical Research (Australasia Branch), Gold Coast, Qld, Australia, December 2015.

Neužil J.: 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.

Kubista M.: 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).

Malý P.: Organizing Committee Member - 15th Asia-Pacific Biotechnology Congress, July 20-22, 2017, Melbourne, Australia.

Bařinka C.: Organizer of the EMBO Young Scientists Forum (EYSF) 2019, Prague. Over 140 participants, focused on PhD students.

Dohnálek J.: Heart of Europe bio-Crystallography meeting, Kutná Hora, 24-26 September 2015, several co-organizers from the institute, 130 participants, international.

Dohnálek J.: International workshop Computational approaches in macromolecular crystallography – Structure refinement at low and atomic resolution, Nové Hrady, 17-19 March 2015, 30 participants, international, several co-organizers from the institute.

Dohnálek J.: Instruct-ERIC workshop Computational Approaches in Integration of Structural Biology Techniques, 8-10 October 2019, IBT Biocev, Vestec, international, 20 participants, lectures – 50 participants.

Dohnálek J. & Schneider B.: Discussions in Structural Molecular Biology in Nové Hrady, several co-organizers from the institute. 2015-2017, 2019, about 120 participants each year, mostly national.

Dohnálek J. & Schneider B.: International workshop Proteins for Life – the 12th P4EU Meeting, 11-12 December 2017, IBT Biocev, Vestec, 50 participants.

Hašek J.: Seminar 301. Meeting of the Czech and Slovak Crystallographic Association, 26 April 2017, IBT Biocev, Vestec, several co-organizers from the institute, 50 participants.

Hašek J.: International conference APERIODIC 2015, Prague Břevnov, 30.8 – 4. 9. 2015. 60 main lectures, 90 posters, published http://www.xray.cz/ms/bul2015-4.htm.

Hašek J.: 15th International Conference on the Crystallisation of Biological Macromolecules, Prague, Pyramida, July 1-5, 2016, http://www.xray.cz/iccbm

Pompach P: 5x Czech Mass Spectrometry Conference 2015-2019. Annual conference, 120 participants, co-organizer. 15-17 April 2015, Hradec Králové, 13-15 April 2016 České Budějovice, 29-31 March 2017, Olomouc, 11-13 April 2018 Prague, 27-29 March 2019 Olomouc.

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