Evaluation of the Research and Professional Activity of the Institutes of the Czech Academy of Sciences (CAS) for the period 2010–2014

Final Report on the Evaluation of the Institute

Name of the Institute: Institute of Molecular Genetics of the CAS, v. v. i.

Fields, in which the Institute registered its teams:

Basic medicine

Observer representing the Academy Council of the CAS: Hana Sychrová
Observer representing the Institute: Vladimír Kořínek, substitute observer Petr Dráber

Commission No. 9: Medical and health sciences
Chair: Prof. Dr. Hans-Georg Joost

Date(s) of the visit of the Institute: November 20 - November 27, 2015
Programme of the visit of the Institute: see attached Minutes from the visit

Evaluated research teams:
No. 1 - Laboratory of Tumour Immunology; No. 4 - Laboratory of Immunobiology; No. 5 - Laboratory of Molecular Pharmacology; No. 9 - Laboratory of Signal Transduction; No. 11 - Laboratory of Molecular Immunology; No. 12 - Laboratory of Biology of Cytoskeleton; No. 19 - Laboratory of Cell Differentiation; No. 21 - Laboratory of Genome Integrity; No. 22 - Laboratory of Transgenic Models of Diseases

Introductory Statement of the Commission No. 9

The commission was very impressed by the generally high quality of biomedical research in the Academy institutes, and identified numerous strengths and opportunities (see individual reports). When we identified weaknesses, we intended to be above all, constructive, and to give external advice to the institutes for their future research strategies. However, the commission has identified structural shortcomings that might require a consideration by the Academy. Therefore, the following summary of general recommendations to CAS precedes each report on the individual institutes, although not all points concerned all institutes evaluated. The commission notes that the Institute of Molecular Genetics has acknowledged and addressed already those points that were within their responsibility.

- **Coherence of the research concepts:** Most institutes and departments pursued a large number of projects that covered a very broad and diverse spectrum of themes. Many projects appeared to have little connection with others, resulting in a fragmentation of the general aims. The commission feels that diversity can be an advantage, when individual projects are of a high quality. However, when projects are not outstanding, diversity weakens the Academy institutes. In the discussion with the researchers, the commission identified the current strategy of funding as a potential reason for the fragmentation: approximately 50% of the funding comes from short-term, non-renewable grants which impairs the pursuit of important, more long-term and ambitious goals.

- **Research on humans:** The commission has asked all institutes for their translation of results into, and their participation in, human research (clinical research, epidemiology). Although there were several promising links and approaches, it seemed that this part of biomedical research needs a particular effort by the Academy. The commission realizes that linking experimental and clinical research is a very difficult task, but is convinced that a thorough discussion of this weakness must be started, and that this should lead to structural changes.

- **External advisory boards:** Most institutes lacked an external scientific advisory board. The commission considers this a particular weakness, and believes that the quality of the academy institutes could be improved by the discussion of all decisions affecting research directions in such a scientific advisory board.

- **Internal discussion and development of the research concepts:** In addition to the lack of a scientific advisory board, the commission identified the lack of other procedures that support the internal development and quality

control of the scientific concepts. As an example, the commission had expected that each institute has a forum where all projects and ideas are discussed by the principal investigators of the institutes (e.g. yearly retreats). The commission also felt that the current decision process for the initiation or termination of projects/units is suboptimal.

- **Training of PhD students within the frame of a Graduate School:** The commission concluded that the participation of students in the research programs of the institutes is overall very good. However, we note that the general training of PhD students could be improved by structures within the Academy institutes (Graduate Schools) that offer a comprehensive training in all research skills, beyond the level of the respective group. Specifically, by this training, all students should become acquainted with the research of the whole institute including concepts, methods and results as well as having direct access to a combination of modern soft skills courses. Thus, building effective Graduate Schools would serve to strengthen the perception that studying for a PhD in a CAS institute indeed represents an attractive contemporary career option for excellent students. Indirectly, such structures would also stimulate exchange and collaboration between groups, possibly also between preclinical and clinical research. The commission learned that Graduate Schools do exist within universities, but feels that the Academy's pursuit of excellence requires a leading role of their institutes in such structures.

A. Evaluation of the Institute as a whole

1. Introduction

The history of the Institute of Molecular Genetics (IMG) dates back to 1953, when the Department of Experimental Biology was established by the Czech Academy of Sciences (CAS). Milan Hasek, who discovered immunological tolerance together with the Nobel Laureates F.M. Burnet and P. Medware, was the first director of this Department that was converted into an Institute in 1962. With the end of the Prague Spring in 1970, Hasek lost his position. Subsequent directors included highly respected scientists who have made seminal contributions. In 1977, the Institute was reorganized and renamed IMG. The main branches of the Institute were housed in two locations between 1964 and 2006. Since 2005, Vaclav Horejsi has been the director of IMG. During his tenure, the previously separated branches were united in

one modern building in 2007. Currently, 477 people (382 FTE), including 149 PhDs, 100 PhD students and 38 MSc students work at IMG. The male/female ratio is approximately 1 and the age structure is optimal. IMG incorporated 23 research laboratories; the following report is based on an assessment of 9 of these units that were subject to this evaluation.

The primary mission of IMG is to aspire to scientific excellence at the international level. The implementation of translational products via spin-off companies is a secondary aim. To fulfil the central mission, IMG has adopted strategies and procedures that can be found in internationally leading scientific institutions. These strategies were highly successful as reflected in numerous important discoveries, and publications in top-rated journals during the evaluation period.

2. Strengths and Opportunities

Scientific excellence - The research topics addressed by IMG are clearly important in the context of international research endeavours and, for the most part, relevant for biomedical science. Several **outstanding papers** have been published in highly respected journals. The long tradition of research at the internationally competitive level fosters high quality, rather than quantity of publications. Publication in high impact journals is reinforced by posting of top-papers along with a congratulatory message from the director at the institutional web site. Such a strategy clearly enhances the competitiveness for obtaining grants and programme projects at the international and national level and contributes to the fact that more than 60% of the IMG budget is currently covered by external funding (mostly grants). The **outstanding scientific reputation** of IMG is reflected in a large number of editorial board memberships and reviewer activities for many journals including Cell, Nature, Science and PNAS. A strong basis for scientific communications has been created by regular institutional seminars, ad hoc lectures of visiting scientists, annual conferences, PhD conferences etc. International collaborations, international employees (currently 15%) and incoming PhD students from foreign countries further promote the exciting and fruitful research environment.

Teaching - The **close collaborations of IMG with universities** are a further strength. Currently, 27 semestral courses at universities are conducted by 7 full and 8 associated professors. The main IMG collaborations are with the Science and Medicine Faculties of Charles University, the Faculty of Biomedical Engineering of the Czech Technical University and the Faculty of Food and Biochemical Technology of the University of Chemistry and Technology in Prague, the Faculty of Science of the University of South Bohemia in Ceske Budejovice, the Comenius University Bratislava and the University of Zagreb. In addition, strong ties with several European Research Institutions are being built. The IMG faculty maintains numerous memberships in field councils of doctoral studies and scientific councils of universities. The intense teaching activities are also evident from a large number of

completed theses of PhD students. In addition, IMG organizes 2-week courses in Advances in Molecular Biology and Genetics for PhD students from IMG and other research institutions and practical courses in microscopic techniques. One faculty member (P. Svoboda) is co-organizer and lecturer of the EMBO Young Investigator PhD student course.

IMG recognizes the importance of **PhD students** as a critical labour force and enrichment for scientific development. Overall, ca. 100 PhD students are engaged in research at IMG and 15-25 students are accepted annually. Detailed procedures are in place to recruit the most talented students. Teaching is not limited to scientific training and education, but comprises formal exercises in complementary skills including publication skills, teambuilding activities, grant writing and career discussions. As training in the latter “soft” skills is a prerequisite for obtaining student and postdoctoral awards from the EU, IMG is in a good position to acquire such support.

Structure and Governance - The structural organisation of the Institute is in line with the realization of the mission and includes, in addition to the **strong scientific leadership by the current director**, a Supervisory Board, an Institute Council and, since 2014, an **International Advisory Board**. Management is straightforward, lean and efficient. IMG is committed to employ highly trained and mobile researchers who are supported by stable core personnel. Clear and effective personnel policies address the age structure, the international qualification of the scientific personnel, hiring and terminating of contracts, methods of evaluation and career development. Contracts of junior and senior group leaders are issued for a period of five years and, dependent on the outcome of internal evaluations, can be prolonged or terminated within or after this period. The main criterion of the internal evaluation is scientific excellence, but additional activities such as teaching, grant support etc. are also considered. These procedures together with stringent quality control management assure an adequate and balanced turnover of research groups which contributes to maintaining a high-quality standard of research and an age-balanced ensemble of group leaders.

Service and Platforms - Strong assets of IMG are numerous platforms and core facilities that support data acquisition by state-of-the-art methods. Platforms include units for media preparation, production of monoclonal antibodies, cryopreservation, X-ray irradiation, structural biology, confocal and electron microscopy, functional genomics and bioinformatics, IT, animal facilities and transgenic mice. The transgenic unit is already very strong, as it offers a complete spectrum of gene editing technologies and will be further strengthened by a comprehensive spectrum of phenotyping methodologies to form the CCP (**Czech Centre for Phenogenomics**). Furthermore, the capacity for confocal/electron microscopy will be enhanced, as the respective unit will be part of the **Czech-BioImaging infrastructure**, which addresses bio-imaging needs at the very advanced level. Another extremely

promising development is **CZ-Openscreen**, a national infrastructure for chemical biology. This unit, which is associated with the laboratory of Cell Differentiation, is a priority project on the Roadmap for Large Research, Development and Innovation Infrastructures of the Czech Republic. The collection of compound libraries is currently extended to encompass 90 000 compounds with previously described biological activities. CZ-Openscreen is equipped with automated robotic stations that are capable of running high-throughput screening using luminescent, fluorescent, AlphaScreen and high-content screening microscopy readouts. Czech and foreign institutions increasingly access the service by this unit. A major effort by IMG relates to the development of the Biotechnology and Biomedicine Center of the Academy of Sciences and Charles University in Vestec (BIOCEV), which was not in operation at the time of the site visit. This new centre clearly has a high potential for elevating the level of science in the Czech Republic.

International Service and Public Outreach - Additional strong points are services for the international science community and IMG outreach activities. IMG researchers created a database for screening the human genome for endogenous retroviruses. The database provides a simple environment that facilitates the characterization of retroviral families and is updated and serviced by a member of IMG. Outreach activities include frequent appearances of IMG researchers on TV and radio stations to discuss science policies and present new scientific developments. IMG approaches the public and prospective students with an IMG Open House Day and IMG researchers have published a number of popular articles in laymen journals and have actively participated in the Week of Science and Technology, organized by CAS. An IMG member created a public educational laboratory termed BIOSKOP that was realized at Masaryk University in 2014. Another IMG member participated in the production of a video of PARP inhibitors and their use as new anticancer drugs.

Regarding benefits for staff, IMG improved working conditions for employees by the introduction of flexible working hours and institutional child day care as well as providing recreation facilities.

Future Research Concept - The research plan of IMG as a whole for 2015-2019 is clearly presented and convincing. The main management priorities will be the development of BIOCEF and further consolidation and improvement of IMG. BIOCEF will house 2 already existing groups and 6 newly established research groups of IMG. Research priorities are built on experience and will increasingly focus on studies of human diseases, thereby placing more emphasis on collaborations with clinical institutions. At the international level, the ties with MPI Dresden will be strengthened and a concept for a temporary exchange of scientific groups between IMG and the University of Cambridge is being developed. Furthermore, efforts will be made to increase the number of foreigners as group leaders. The instalment of an IMG fellowship for the near future is well conceived.

3. Weaknesses and Threats

The commission identified only few potential weaknesses. (1) While IMG offers many opportunities for scientific discussions, a formal forum where all principle investigators discuss the current research concepts, current and emerging technologies and strategies. Such a forum (e.g. yearly retreats) could be the basis of the future scientific development of the Institute towards new fields and approaches. (2) Some departments would benefit from interactions with clinical research. (3) A potential threat for IMG is the upcoming retirement of the current director. (4) Another potential threat relates to the sustainability of funding BIOCEF.

4. Recommendations

The commission recommends a yearly retreat (1-2 days), where the entire faculty can discuss emerging fields and technologies that may influence the overall strategy. The commission also recommends that the Institute discuss ways to strengthen the cooperation with clinicians. Otherwise, keep going with the same winning formula!

5. Detailed evaluations

Declaration on the quality of the results and share in their acquisition
The commission concludes that the quality of results of the Institute is overall **very good and in large parts excellent**. In collaborations, the contribution of the Institute is always essential, and the Institute is often the leading partner.

Declaration on the involvement of students in research
The commission considers the involvement of students in research very good. Their contribution to the success of the Institute is vital and creates a very positive and creative atmosphere.

Declaration on societal relevance
The commission concludes that the activities of IMG are of very high societal relevance.

Declaration on the position in the international and national context
The commission concludes that the position of IMG is internationally competitive and, in some parts, leading. The commission felt that IMG is a “Flagship” institution of Czech science and a particular asset to CAS.

Declaration on the vitality and sustainability
The commission concludes that the vitality and sustainability of IMG is high.

Declaration on the strategy and plans for the future

The commission concludes that strategy and plans for the future are very good and absolutely convincing.

6. Evaluation of the individual teams

Evaluation of the Team No. 1: Laboratory of Tumour Immunology

1. Introduction

The status of the Laboratory of Tumour Immunology led by Milan Reinis had been changed in 2015 - from an independent research lab to a service immunology group within the Phenotyping Module of the Czech Centre for Phenogenomics (CCP; within the BIOCEV project). The IMG Council based this decision on the results of the CAS evaluation in 2010, and on a subsequent thorough examination and consideration. It was concluded that in spite of the good publication activity, the qualities and perspectives of the group were not sufficient for an independent status as a research group. There were problems with the age structure of the group and a high dropout rate of students. The quality of the research concept, as presented by the group leader, was not convincing. However, the members of that group, including Dr. Reinis, have valuable skills in tumour immunology and preclinical mouse models. Thus, the Laboratory was closed, and the personnel was transferred to the Phenotyping Module of the Czech Centre for Phenogenomics.

Because of this status change, the commission decided to evaluate the Laboratory of Tumour Immunology solely on the basis of the documents provided.

2. Strengths and Opportunities

As a result of its evaluation, the commission supports the decision of the Institute to close the Laboratory of Immunology, and concludes that its transfer has the potential to considerably enhance the potential of the Phenotyping Module of the CCP.

3. Weaknesses and Threats

As a general threat to the Czech Centre for Phenogenomics service unit, the commission identified the financing modalities for collaborations, which might lead to underfunding of other projects.

4. Recommendations

In the evaluation of the Laboratory of Transgenic Models of Disease, it was recommended that the CCP service unit increase the financial contributions recovered from the collaboration partners. This recommendation is relevant also for the transferred group, which will introduce additional traits into the phenotyping programme of the service unit.

5. Detailed evaluations

Because of the closure of the Laboratory of Tumour Immunology, no detailed evaluations of previous performance and future concepts were performed.

Evaluation of the Team No. 4: Laboratory of Immunobiology

1. Introduction

The laboratory was established in 2007, when the group leader Dominik Filipp moved from Toronto, where he undertook long-term postdoctoral studies, to Prague. The Department comprises 3 full-time researchers, 4 PhD students, 2 undergraduate students and 1 technician. Methods used include DNA recombinant technologies, standard biochemical and cell biology methods, a vast array of immunological techniques and advanced microscopy. Furthermore, the laboratory has succeeded in generating transgenic, knockout and knock-in mice and hematopoietic chimeras.

Initial studies addressed the role of autoimmunity in type 1 diabetes (Eur J Hum Genet. 2012;20:457-62, Scand J Immunol 2012;75:210-19, J Diabetes Res 2013; 589451). Subsequently, the main research focus of the laboratory shifted to central and peripheral immunological tolerance, TCR proximal signalling and early haematopoiesis. Immunological tolerance has been addressed in an excellent recent publication. Studies in autoimmune regulator (AIRE) deficient mice, used as a model system, showed that loss of AIRE-mediated immune tolerance against defensins resulted in the intestinal disorder observed in patients with APECED (Gastroenterology 2015;149:139-50). The group also contributed to research related to Wnt signalling in the small intestine (Cell signalling 2015;27:245-56, Molecular Cancer Res, accepted for publication). The group has published several manuscripts on proximal TCR signalling (Immunol Lett 2012;142:64-74, Immunol Cell Biol 2015;93384-95). Additional studies suggest that TLR2 positive progenitors contribute to primitive and also to definitive haematopoiesis (manuscript in revision). Finally, work is also directed towards the role of oligofuranosides in the induction of cytokine production and/or maturation of antigen presenting cells.

The current research team appears to be stable and no major changes in personnel are expected for the next two years. The research activities appear to be somewhat limited, as several grants will have to be written to secure funding for the coming years. The laboratory entertains strong collaborations with Ludger Klein (LMU Munich), who is a leader in the field. This collaboration is supported by a bilateral travel grant for members of both laboratories. Informal working relationships exist with other well-established scientists in Canada, Norway, Finland and Israel.

The group leader teaches a full course on innate immunity at the Department of Cell Biology and Immunity, Faculty of Life Sciences, Charles University for undergraduate and graduate students. This course is also included in the Erasmus exchange programme.

The group leader and members participate in other courses at Charles University and the group leader also teaches at Comenius University in Bratislava. Group members actively participated in public communications and outreach activities such as “The Week of Science and Technology”. One article in the popularization journal Vesmir was published in 2013.

The research plan of the team for 2015-2019 is convincingly described and is based on hypothesis-driven research in the topics described above. The proposed studies are expected to provide a deeper understanding of cellular, molecular and signalling aspects of peripheral tolerance. Experimental strategies will heavily rest on transgenic animals that are mainly generated in house. Substantial preliminary data have been obtained to support the rationales of the proposed studies.

2. Strengths and Opportunities

The research addresses innovative concepts of clinical relevance. A very positive team atmosphere and a positive trajectory of publishing activities are evident. The team seems to be competent and in command of many techniques. The collaborations with leaders in the field are certainly beneficial for the further development of the group. The SWOT analysis of the group by the team leader is realistic and credible.

2. Weaknesses and Threats

Given the size of the Laboratory, it may have initiated too many distinct projects which could be underfunded and understaffed.

4. Recommendations

In the opinion of the commission, the group should be supported and encouraged. Interaction with clinical departments should be intensified and contacts with industry may be established regarding possible drug targets and potential funding. International visibility may be increased by more frequent participation in conferences, and in enhanced reviewing and editorial activities.

5. Detailed evaluations

Declaration on the quality of the results and share in their acquisition

The commission concludes that the quality of results is overall very good. In collaborations, the contributions of the group are essential.

Declaration on the involvement of students in research

The commission considers the involvement of students in the research very good.

Declaration on societal relevance

The commission considers the societal relevance of the research programme high.

Declaration on the position in the international and national context

The commission concludes that the Department is internationally visible and nationally leading.

Declaration on the vitality and sustainability

The commission concludes that vitality and sustainability are very good.

Declaration on the strategy and plans for the future

The commission concludes that the strategy and plans for the future have been clearly presented and were convincing.

Evaluation of the Team No. 5: Laboratory of Molecular Pharmacology

1. Introduction

The Laboratory of Molecular Pharmacology comprises a small group (2 PhDs, 3 PhD students and 2 technicians) that decreased in size during the past years for financial and personal reasons. Methods used include protein chemistry, recombinant DNA technologies, immunohistochemistry, functional pharmacological assays, bio-fluorescence resonance energy transfer assays (BRET, FRET) and knockout and knock-in transgenic mouse models.

The main research activities concentrate on the principles of metabotropic glutamate receptor (mGluR) activation and signalling, the subunit composition of mGluR1 and the regulation of cannabinoid receptor 1 signalling via a novel interactor SGIP1. mGluRs are G-protein coupled receptors (GPCrs) that are members of the class C family that operate as dimers. In a collaborative effort with the University of Würzburg, the group performed elegant studies on activation dependent inter- and intra-subunit conformational changes, using fluorescent fusion proteins. The model deduced by these studies indicates that after initial conformational changes in the extracellular ligand binding domain and a relative movement of the transmembrane regions, the heptahelical transmembrane region of only one subunit undergoes a conformational change that activates G-proteins (Scie Signal 2012;5(237), ra59). mGluR1 occurs in 2 isoforms termed R1a and –b. The b-isoform is encoded by an alternatively spliced transcript and is characterized by a short intracellular domain that lacks an ER retention signal. The group has now clearly demonstrated that 1a/1b heterodimers can occur *in vivo* which has a number of potential implications (Neuropharmacology 2014;86:329-36).

Additional manuscripts included studies linking IL1RAPL1 mutations to a postsynaptic signalling pathway (Curr Biol 2010;20:103-15) and collaborative studies on the transcriptional regulation of various nuclear receptors (Biochem Pharmacol 2010;79277-

87, J Thromb Hemost 2011;12:2708-17). More recently, interesting data on cannabinoid receptor 1 (CB1R) signalling were obtained (unpublished). Using a yeast two-hybrid system, they identified Src homology 3 domain growth factor receptor-bound 2-like (endophilin) interacting protein 1 (SGIP1) as a novel interaction partner for the C-terminal region of CBR1. Preliminary studies showed that SGIP1 mediates cell surface stability of activated CB1R, and affects specific signalling cascades of CB1R. Thus, it will be possible to dissect distinct CB1R signalling pathways, study their cellular consequences and develop specific ligands.

The research group has several international collaborations with renowned institutions including CNRS Montpellier, the Institute of Pharmacology and Toxicology, University of Würzburg, NIDCD/NIH Bethesda, CNR Neuroscience, University Milan, Institute Carlo Besta, Milan and others. The Institute implemented several new technologies to measure functional pharmacological responses. In house collaborations provide advanced microscopy methods as well as animal models generated by gene editing. Funding of research activities has now been improved and a former PhD student obtained an EMBO fellowship.

The group leader is associate professor and gives lectures to medical students at the 2nd Faculty of Medicine, Charles University in Prague. BSc, MSc and PhD students (1/2/4) were supervised between 2010 and 2014 and 2 PhD and 2 MSc students defended their theses. The group leader contributed several chapters to the textbook “Biopharmaceuticals” (Grada Publisher 2012).

The research plan for the team includes studies on the regulation of the signalling cascades of mGluRs and the molecular mechanisms whereby SGIP1 affects CB1R signalling. The plan reflects a logical extension of the previous studies, is based on new preliminary data and is convincing.

2. Strengths and Opportunities

The leader of the laboratory is competent and his publications are recognized as reflected by many citations. Strong collaborations with other European Institutions are in place. The research methods are state-of-the-art in the field of receptor research. The discovery of SGIP1 as a CB1R-interacting protein is a substantial finding that may provide new and important aspects of CR1B signalling.

3. Weaknesses and Threats

The small size of the group may limit its research activities. Translational aspects are not fully exploited.

4. Recommendations

The translational potential could be strengthened and the original and innovative aspects of the projects should be pursued with high priority. Scientific activities that increase the visibility of the group should be enhanced.

5. Detailed evaluations

Declaration on the quality of the results and share in their acquisition
The commission concludes that quality of results is very good. Their share in the acquisition is high; in collaborations, the group always contributed essential ideas and data.

Declaration on the involvement of students in research
The commission considers the involvement of students in research good.

Declaration on societal relevance
The commission concludes that the research of the group is of societal relevance.

Declaration on the position in the international and national context
The commission concludes that the Department is internationally competitive and nationally leading.

Declaration on the vitality and sustainability
The commission concludes that the vitality and sustainability is good.

Declaration on the strategy and plans for the future
The commission concludes that strategy and plans for the future are logical and sound.

Evaluation of the Team No. 9: Laboratory of Signal Transduction

1. Introduction

The aim of the Laboratory is to understand early signalling pathways activated by cell surface receptors, with a focus on protein complexes at the inner membrane surface (signalosomes). Specifically, the group has identified novel signalling components of the mast cell-related receptors FcεRI. The group employs state-of-the-art methodology in their functional and biochemical analysis of the mast cells (e.g. assays of chemotaxis, FRET for the study of protein interaction). Both in-vitro and in-vivo models are investigated. As suitable models, mast cells with altered gene expression and transgenic mice (knockout, lentiviral gene transfer, knockdown with

siRNA). With this approach, the Laboratory is in a unique position to find novel strategies for the treatment of allergies, and to generate commercializable products.

The Laboratory is well supported by grants from the GACR. It is partner in the EU COST action 'Cell signalling in mast cells'. Links with international research institutions are strong: Joint papers have been published with the Broad Institute (Harvard), the Hebrew University (Israel), INSERM (France), Karolinska Hospital (Sweden), and the Charité (Germany).

The group collaborates with the business sector and actively seeks to commercialize products (e.g. mutant Taq polymerase) in an IMG spin-off company. Other products include anti-taq polymerase aptamers. The group is developing novel in vivo analysis technology such as the 'Passive systemic anaphylaxis (PCA) assay'.

2. Strengths and Opportunities

(1) The commission was impressed by the competence and strong publication record of the team.
(2) The research concept has a proven, very high translation potential.
(3) The Laboratory plans beyond the biochemical and experimental concepts, and pursues ideas originating from clinical problems.
(4) Many European connections have led to collaborations and joint papers.
(5) The group actively develops commercializable products and assays.

3. Weaknesses and Threats

As a potential threat for the group, the commission identified the age distribution of its investigators with a trend towards the senior generation. Furthermore, there might be a tendency towards too high diversification in the studies of the signalling systems.

4. Recommendations

The commission recommends that the Laboratory should try to establish additional models that offer a high relevance for the human situation (e.g. human cell lines). In addition, the group is encouraged to further strengthen collaborations with domestic clinicians.

5. Detailed evaluations

Declaration on the quality of the results and share in their acquisition
The commission concludes that the results of the Laboratory were overall very good. In the majority of the collaborations, the group was leading partner; in all others it provided essential contributions.

Declaration on the involvement of students in research
The commission concludes that the involvement of students (6 PhD students, 2 MSc students) in the research is overall good.

Declaration on societal relevance
The commission considers the societal relevance of the research aims very high.

Declaration on the position in the international and national context
The Laboratory is internationally competitive, and nationally leading.

Declaration on the vitality and sustainability
The commission identified the age distribution of the scientists as a potential problem.

Declaration on the strategy and plans for the future
The commission concludes that the research strategy and the future plans are logical and absolutely convincing.

Evaluation of the Team No. 11: Laboratory of Molecular Immunology

1. Introduction

The research focus of the Laboratory of Molecular Immunology is similar and complementary to that of the Laboratory of Signal Transduction. Specifically, the Laboratory investigates signalling pathways of T-cell receptors, with a focus on lipid raft-associated signalling proteins, and transmembrane adaptor proteins (TRAPs). The group uses state-of-the-art methodology in their analysis of T-cell function. Both human and mouse cells as well as in-vivo models are investigated. As suitable models, T cells with altered gene expression as well as transgenic mice are employed. With this approach, the Laboratory aims to find novel strategies for modulation of T cell function (e.g. chimeric antigenic receptors), and to generate commercializable products. Because of the upcoming retirement of its head, the Laboratory was split into three scientifically independent but closely collaborating groups (Leukocyte signalling, Haematooncology, Molecular Immunology).

The Laboratory is well supported by grants from the CSF. The publication record of the group is strong. International collaborations are also strong: Joint papers have been published with the UCSF (USA), the DKFZ (Germany), the Harvard Stem Cell Institute (USA), the Hebrew University (Israel), and others.

The group collaborates with the business sector and actively seeks to commercialize products (e.g. monoclonal antibodies); this activity has already generated a modest income from licences.

2. Strengths and Opportunities

The commission identified as strengths:
(1) the competence of the team that has a clear vision, (2) a strong record of publications in highly respected journals, (3) the high international reputation of the group, and (4) the research focus on central mechanisms of T-cell function with a promising translational perspective.

3. Weaknesses and Threats

The commission identified the upcoming retirement of the head of the Laboratory, and the consequently implemented structural changes as a potential threat, if the newly formed groups lack a critical mass.

4. Recommendations

The commission recommends that the group further strengthens collaborations with clinicians and tries to receive input from the clinical perspective in order to enhance the translational potential of its research.

5. Detailed evaluations

Declaration on the quality of the results and share in their acquisition
The commission concludes that the results of the Laboratory were overall very good. In a large part of the collaborations, the group was leading partner; in all others, it provided essential contributions.

Declaration on the involvement of students in research
The commission concludes that the involvement of students (4 PhD students, 2 MSc students, 1 BSc student) in the research is overall good.

Declaration on societal relevance
The commission considers the societal relevance of the research aims very high.

Declaration on the position in the international and national context
The Laboratory is internationally competitive, and nationally leading.

Declaration on the vitality and sustainability
Vitality and sustainability of the Laboratory are high. However, the commission identified the age structure (upcoming retirement of the group leader and the consequent re-organization of the Laboratory) as a potential problem.

Declaration on the strategy and plans for the future
The commission concludes that research strategy and future plans are absolutely convincing and demonstrate a clear vision.

Evaluation of the Team No. 12: Laboratory of Biology of Cytoskeleton

1. Introduction

Structure- function-relationships of microtubule (MT) proteins and their interaction with other factors of the cytoskeleton are the long-term research interest of the group headed by Pawel Draber. Research methods include biochemical and immunochemical techniques, standard molecular and cell biology procedures, light and electron microscopy, time lapse imaging and quantification of microtubule dynamics. Studies were conducted in human and mouse cell lines, mast cells and gliomas. Specific research topics addressed MT reorganization in activated cells, the regulation of MT nucleation, new function for gamma-tubulins and MT dysregulation in cancer cells.

As MTs are involved in the degranulation of mast cells, mechanisms that control MT arrangements were studied in bone-marrow derived mast cells. Activation of mast cells was shown to be associated with the formation of membrane protrusions that contained MTs. This process required intact stromal interacting molecule 1 (STIM1) which is involved in intracellular Ca^{++} flux (J Immunol 2011;186:913-23). They further showed that the concerted action of tyrosine kinases, β PIX/GIT1 proteins and Ca^{++} serve in the propagation of signals that regulate MT nucleation in activated mast cells (J Immunol 2015;194:4099-111). In an effort to identify new functions of γ-tubulin, the researchers convincingly demonstrated that γ -tubulin is present in the nucleoli of mammalian interphase cells. Furthermore, γ -tubulin was found to be associated with the tumour suppressor protein C53 and overexpression of γ-tubulin antagonized the inhibitory effect of C53 on DNA damage G2/M checkpoint activation (J Cell Physiol 2012;227:367-82).

The 2 γ-tubulins (termed 1 and 2) that are encoded by two distinct genes are highly homologous (97% sequence identity). Studies in knock-out mice have shown that γ-tubulin 1 deficient mice die at the blastocyst stage, while γ-tubulin 2 deficient mice develop normally, suggesting that γ-tubulin 2 cannot substitute for γ-tubulin 1. Studies by the group showed, however, that γ-tubulin 2 rescues γ-tubulin 1 knock-down in cultured cells and that γ-tubulin 2 is expressed in blastocysts at very low levels. Thus, the γ-tubulins are redundant with respect to nucleation activity and the lack of γ-tubulin 2 to effectively substitute for γ-tubulin 1 deficiency during embryogenesis is the result of very low levels of expression at the blastocyst stage (PLoS one 2012; e29919). To distinguish γ-tubulin 1 from γ-tubulin-2 expression, monoclonal antibodies were developed that were specific for γ-tubulin 1. Expression studies in a neuroblastoma cell line indicated that the regulation of expression of the two γ-tubulins differs, as γ-tubulin 2 accumulated in mature neurons (Mol Biol Cell 2014;25:108-9, P144). In medulloblastomas and non-small cell lung cancer, the expression of both γ-tubulins was increased suggesting that they may serve as prognostic markers (J Cell Physiol 201,223:519-29, Histology and Pathology 2012;27:1183-94). In glioblastoma cells and

cell lines, the MT destabilizing ATPase spastin was increased in comparison to non-neoplastic tissue. Spastin depletion reduced cell motility and cell proliferation in glioblastoma cell lines. Hence, spastin may be targeted to reduce glioma cell invasion (J Neuropath Exp Neurol 2011;70:811-26). A related avenue of research was directed towards the development of new research tools and methods. A procedure was developed for freeze-drying and rehydrating assembly competent tubulin or MTs that can be used for *in vitro* and *in vivo* assays (Anal Biochem 2010;397:67-72, Methods Mol Biol 2014;1129:443-458). Sensitive assays were developed for quantification of tubulin in complex biological fluids (J Immunol Methods 2013;395:63-70) and measurement of the tau protein, used as biomarker for Alzheimer's disease (J Immunol Methods 2014;406:137-142). Overall, the group published 16 original research papers, 2 book chapters and several review articles related to MT, the cytoskeleton and gliomas. Other scientific activities of the group included presentations at international and national scientific meetings.

The research group had major collaborations with Drexel and Temple Universities, both in Philadelphia, the University of Illinois in Chicago, the Leibnitz Institute for Age-Research in Jena, Clinical Laboratories of the Faculty Hospital Brno and the Third Faculty of Medicine, Charles University. Within IMG, major collaborative efforts included the Departments of Biology of Cell Nucleus and Signal Transduction. The group demonstrated stability in personnel and funding was adequate during the evaluation period.

The group leader held a course on "structure and function of cytoskeleton" at the Faculty of Science, Charles University, as well as lectures in other courses for undergraduate and graduate students. He served as board member of study programme committees and hosted 3 BSc, 2 MSc and 4 PhD students. Thesis defences included 3,1, and 2 for BScs, MScs and PhDs, respectively.

The group leader holds several Editorships and served as reviewer for many scientific journals and Czech granting agencies. He is a member of the European Cytoskeleton Forum. Group members participated in local scientific committees. Communication with the public and outreach activities included the initiation of a WIKIpedia-like activity of European Mast Cell and Basophil Research Network, several press releases, presentations and other activities at science festivals.

The research plan builds on previous research activities and includes the role of signalling proteins in microtubule organization, the relevance of the interaction of the tumour suppressor protein C53 with UFL1, a novel type of E3 ligase involved in cell cycle progression as well as studies on MT regulating proteins in gliomas. Furthermore, the group intends to participate in a H2020 project entitled "Common mechanisms of mast cell activation driven diseases and their related co-morbidities". For this project, preliminary data have been obtained rendering the research plan credible.

2. Strengths and Opportunities

The research group has a sound publication record and has a competent leader.

3. Weaknesses and Threats

Innovative aspect of the research could be improved by taking advantage of the IMG infrastructure and capitalisation thereof.

4. Recommendation

In some of the projects, transgenic mice should be considered as suitable models. The interactions with clinical departments should be intensified, and interactions with the business sector should be increased.

5. Detailed evaluations

Declaration on the quality of the results and share in their acquisition

The commission concludes that the quality of results is overall very good. In collaborations, the contribution of ideas and data by the group is essential.

Declaration on the involvement of students in research

The commission concludes that the involvement of students in the research is very good.

Declaration on societal relevance

The commission considers the societal relevance high.

Declaration on the position in the international and national context

The commission concludes that the Department is internationally visible and nationally leading

Declaration on the vitality and sustainability

The commission considers vitality and sustainability of the group very good.

Declaration on the strategy and plans for the future

The commission concludes that strategy and plans for the future have been presented clearly, and are convincing.

Evaluation of the Team No. 19: Laboratory of Cell Differentiation

1. Introduction

The main research concentrates on the molecular mechanisms of cell fate determination. Tools and models have been established to study self-renewal and differentiation of haematopoietic, neural and mesenchymal stem cells. Growth factors and a more

systematic approach with chemical compounds are used to influence/perturb the respective pathways.

The group extended studies of vertebrate hematopoietic development to the zebrafish. They generated several zebrafish growth factors and performed clonal myeloerythroid precursor assays in semisolid media. Granulocyte colony-stimulating factor (Gcsf) was found to drive the differentiation of granulocytes, monocytes and macrophages. In addition, clonogenic and proliferation capacities of bipotent thrombo/erythropoietic progenitors were analysed for comparison with mammalian counterparts. These studies strongly suggested the evolutional conservation of the principal mechanism in haematopoiesis despite phenotype differences between fish and mammalian end products (Blood 2011;118:1274-82, Blood 2013;122:3918-28, Blood 2014;124:220-8).

With respect to neural differentiation, the group studied Disp3, a family member of Dispatched that contains a sterol-sensing domain and is mainly expressed in the brain and retina. Disp3 co-localises with cholesterol in the endoplasmic reticulum and is positively regulated by T3. High expression levels were observed in primary human brain tumours. Ectopic expression of Disp3 promoted proliferation and reduced neural differentiation (FEBS Lett 2014;5884071-7).

As pathways in stem cell biology are often dysfunctional in cancer cells, high throughput screening was used to identify agents that could sensitise/modulate such pathways. Homoharringtonin (HHT), previously tested as an anti-leukaemia drug, was identified as an efficient enhancer of TRAIL-mediated apoptosis in TRAIL-resistant colorectal cancer cells suggesting its potential application in anti-cancer combination therapy (Apoptosis 2013;18:730-50). Furthermore, monensin, a natural ionophore antibiotic, was identified as a potent inhibitor of Wnt-signalling. The drug was tested in mammalian cells, zebrafish and Xenopus embryos and suppressed progression of intestinal tumours in mouse models (Mol Cancer Ther 2014;13:812-22).

In other studies, novel oestrogen receptor modulators were characterized and activities of steroid analogues were profiled (J Med Chem 2010;53:6947-53, J Med Chem 2010;53:7884-94, J Organometal Chem 2013;747:178-83) and several new assays applicable to high-throughput screening were developed (Comb Chem High Throughput Screen 2011;14:248-66, J Biomol Screen 2012;17:1030-40, J Med Chem 2011; 54:7884-98).

Overall, the Department has published 18 papers during the evaluation period. In addition, several patents were filed and applications to the Patent Cooperation Treaty were submitted. The laboratory has a number of collaborations at the national and international level and funding has been adequate for the past.

Several group members were active in academic teaching. The group leader Petr Bartunek lectured in PhD courses in Molecular Biology and Genetics and supervised

bachelor, Diploma and PhD students. J. Jindrich is associate professor at the Department of Organic Chemistry, Faculty of Science, Charles University, where he is head of the Group of Supramolecular Chemistry. He lectured in several courses and organized exercises in Organic Chemistry. D. Svozil lectured at the Institute of Chemical Technology, Prague. Overall supervision included 10 BSc, 4 MSc and 11 PhD students. The numbers of thesis defences were 10, 7 and 4 for BScs, MScs and PhDs, respectively.

P. Bartunek is a panel member of the Czech Science Foundation and secretary and board member of the International Chemical Biology Meetings. He reviewed articles for Experimental Hematology and J. Med. Chem. D. Svozil and J. Jindrich were also involved in several activities relevant for the Science community.

The research plan represents a logical and convincing extension of previous research and focuses on a deeper understanding of the role of Disp3 in developing neural cells, on the development of erythroid cells in vertebrates, generation of blood from human pluripotent stem cells, on the role of steroid receptors in breast and prostate cancer and on further development of zebrafish as a model for human diseases.

CZ-OPENSCREEN

This platform addresses the needs of the interdisciplinary arena of chemical biology, which studies cellular and organismal responses to chemical compounds with the ultimate goal to develop new analytical tools and to discover new small molecules for treating human diseases. CZ-OPENSREEN is one of the priority and strategic projects of the Roadmap for large Research, Development and Innovation infrastructure in the Czech Republic and serves as national node for the pan-European EU-OPENSCREEN. The platform is located in a separate building and is associated with the Laboratory of Cell Differentiation. Major activities were devoted to the development of the informatics infrastructure and a state-of-the-art platform that is suitable for executing a broad portfolio of high-throughput miniaturized assays. This platform starts with kinetic biochemical assays and extends to multiplex high-content experiments. However, high-content screening imaging needs further custom-designed development, as current methods rely mainly on commercially available solutions. Currently, two integrated and fully automated robotic stations are available with a range of instruments such as liquid handlers, washers, plate sealers, dispensers, plate readers etc. The use of zebrafish is of vital strategic importance. The chemical libraries have now been increased to encompass a total of >90 000 compounds. The user community is mainly recruited from academia and small medium-sized enterprises. Access is based on a collaborative basis and/or open access. Around 50 screens have been performed so far, but lead compounds have not yet been identified.

2. Strengths and Opportunities

Competent and dynamic leadership is well demonstrated. The group performs high quality research, uses innovative models and produced several patents and products.

The technology platform for chemical biology is highly visible at the national and international level and the evident popularity of the open source LIMS database is clearly valuable. The age spectrum of group members is good. Funding seems to be very good.

3. Weaknesses and Threats

The commission identified the combination of service and investigator-driven research in one unit as a potential threat. It has to be excluded that insufficient funding of the service part jeopardizes the independent research projects.

4. Recommendations

The Laboratory should consider a participation in public communication and outreach activities.

5. Detailed evaluations

Declaration on the quality of the results and share in their acquisition

The commission concludes that the quality of results are overall very good and, in part, excellent. In collaborations, the Laboratory is frequently the leading partner; in all others it contributes essential ideas and data.

Declaration on the involvement of students in research

The commission considers the involvement of students in the research activities very good.

Declaration on societal relevance

The commission considers the social relevance of the research programme high

Declaration on the position in the international and national context

The commission concludes that Department is internationally competitive and nationally leading.

Declaration on the vitality and sustainability

The commission considers vitality and sustainability of the group very good.

Declaration on the strategy and plans for the future

The commission concludes that strategy and plans for the future have been clearly presented and are absolutely convincing.

Evaluation of the Team No. 21: Laboratory of Genome Integrity

1. Introduction

The Laboratory investigates of cellular response to DNA damage in relation to cancer and ageing. Specific aims were the mechanisms of cellular senescence, DNA

damage signalling and repair, and cell cycle control. Furthermore, the group develops new therapeutic strategies based on gold microrods, and on approaches to overcome radio- and chemoresistance of tumours. The group takes advantage of a broad range of methods and models including cell lines, mouse models and also material from patients. The head of the Laboratory is one of the most respected scientists in DNA damage research worldwide. He has a double appointment (Copenhagen and Prague) which inevitably limits his presence in Prague. However, the commission was convinced that this limitation is by far outweighed by the benefits of the double appointment. Also, during his absence, Prof. Bartek keeps close contact with his excellent deputies by frequent video conferences.

The Laboratory is well supported by grants from the GACR. The publication record of the group is outstanding; its publications were frequently cited. International collaborations are also strong: Joint papers have been published with the University of Copenhagen (Denmark), EMBL (Germany), the Institute of Cancer Research (London), the University of Zurich (Switzerland), and others. The group collaborates with clinical research units at the VAMC New York, the Rigshospitalet Kopenhagen, St. Jude Children's Hospital Memphis, and at hospitals of Charles University Prague.

2. Strengths and Opportunities

The commission identified as strengths
(1) the outstanding competence and recognition of the scientists of the group, (2) the outstanding importance and quality of the research programme, (3) the active pursuit of its high translational potential, and (4) the outstanding publication record, international recognition and collaborations of the Laboratory.

3. Weaknesses and Threats

As a potential weakness, the commission identified the limited time Prof. Bartek can devote to the group in Prague. A potential threat would result from his retirement which will require an external recruitment and/or a major rearrangement of the Laboratory.

4. Recommendations

The commission feels that the Laboratory is presently well on track and has no recommendations except to keep an eye on the potential weakness and threats.

5. Detailed evaluations

Declaration on the quality of the results and share in their acquisition

The commission concludes that the Laboratory has an outstanding publication record, and that the quality of the results was overall excellent. In a large part of the collaborations, the group was leading partner; in all others, it provided essential contributions.

Declaration on the involvement of students in research
The commission concludes that the involvement of students (16 PhD students, 7 MSc students, 12 BSc student) in the research of the Laboratory is excellent.

Declaration on societal relevance
The commission considers the societal relevance of the research programme very high.

Declaration on the position in the international and national context
The commission concludes that the Laboratory is internationally and nationally leading. The Laboratory is a flagship of cancer research in the Czech republic, and an asset to the Academy.

Declaration on the vitality and sustainability
Vitality and sustainability of the Laboratory are very high. However, the commission identified the potentially upcoming retirement of the Laboratory chief (and consequent re-organization of the Laboratory) as a potential problem.

Declaration on the strategy and plans for the future
The commission was very much impressed by the research concept of the Laboratory. Strategy and the future plans were fully convincing and demonstrated a clear vision of very important aims.

Evaluation of the Team No. 22: Laboratory of Transgenic Models of Diseases

1. Introduction

The Laboratory of Transgenic Models of Disease combines a research team and a service unit (CCP, Czech Centre for Phenogenomics). The research unit employs transgenic mouse models for rare and Mendelian diseases. In addition, it investigates stem cell pluripotency and early embryonic development. The CCP develops technologies for gene targeting, and provides service for generation and phenotyping of transgenic mice. Currently, 50% of the collaborations of CCP are international, 5-10% are from other academy institutes.

2. Strengths and Opportunities

(i) The Laboratory effectively pursues its own excellent projects and provides of an attractive and advanced service with cutting edge technology. The service unit is one of 5 comparable centres in Europe. (ii) The Laboratory has numerous international collaborations with leading groups; there were 130 requests including 80 for the generation of transgenic mice. (iii) The personnel of the Laboratory have a proven record of expertise in all novel transgenic methods, and have the ideal age distribution.

3. Weaknesses and Threats

The commission sees the financial modalities as a potential threat. So far, most service projects for external research groups were conducted on a collaborative basis. Consequently, the costs of these projects were not fully covered by the external partners. This model of financing could ultimately render the in-house projects of the research unit underfunded and jeopardize their quality.

4. Recommendations

The commission recommends that the service unit CCP tries to recover a higher share of the costs from the collaboration partners.

5. Detailed evaluations

Declaration on the quality of the results and share in their acquisition
The commission concludes that the quality of the results is overall very good and in some parts excellent. In collaborations, the Laboratory always provides essential contributions and is in some projects the leading partner.

Declaration on the involvement of students in research
The commission considers the involvement of students in the research of the Laboratory very good.

Declaration on societal relevance
The commission concludes that the societal relevance of the research is high.

Declaration on the position in the international and national context
The research of the Laboratory is nationally leading and internationally recognized. The work of the service unit Czech Centre for Phenogenomics is internationally competitive and nationally unique.

Declaration on the vitality and sustainability
The commission concludes that the vitality and sustainability of the unit is very good.

Declaration on the strategy and plans for the future
The presentation of future research plans was convincing and clear. The commission considers these plans to be of highest quality.

Date: December 21, 2015

Commission Chair: Prof. Dr. Hans-Georg Joost