

# **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 Physiology of the CAS

**Fields in which the Institute registered its teams:**

Basic medicine, Health sciences, Medical biotechnology and medical engineering

Observer representing the Academy Council of the CAS: Hana Sychrová

Observer representing the Institute: Ladislav Vyklický, substitute observer Jiří Pácha

**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 - Experimental Hypertension; No. 5 - Adipose Tissue Biology; No. 7 - Biomaterials and Tissue Engineering; No. 8 - Cellular and Molecular Neuroendocrinology; No. 9 - Cellular Neurophysiology; No. 10 - Epithelial Physiology; No. 11 - Functional Morphology; No. 13 - Cardiovascular Morphogenesis; No. 15 - Neurochemistry; No. 16 - Neurophysiology of Memory; No. 17 - Neurohumoral Regulations; No. 20 - Developmental Epileptology; No. 21 - Developmental Cardiology; No. 22 - Biochemistry of Membrane Receptors*

## 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. These points concerned almost all institutes evaluated by the commission. Therefore, the following summary of general recommendations to CAS precedes each report on the individual institutes.

- **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 would 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 Institute of Physiology, CAS is the Czech republic's leading institution in the field of normal and pathological physiology. It dates back to 1954 when it was founded under the directorship of Professor Zdenek Servit (1954-1969) together with Professors Arnost Gutmann, Jiri Krecek and Otakar Poupá. The expertise of these founders naturally focused research in the Institute towards Neurophysiology, Muscle regeneration, Heart adaptation to hypoxia and Ontogenesis. Thus, initially the Institute consisted of 4 departments until it was radically reorganized in 1980 to create 2 "sectors" (Neuroscience and Developmental Physiology). However, after the national political changes in 1989, the structure of the Institute was altered once again to create the existing structure. The overall aim over the past six decades has been to characterize basic biological mechanisms and to thereby help public health by improving prevention, diagnosis and treatment of serious diseases states. Currently, the main areas of interest are organized around three axes: Neurophysiology, Cardiovascular Physiology and Metabolism. The work of the Institute spans all levels of physiological research from the systems level to cellular and molecular analysis, and this multidisciplinary approach generates an essential synergy within the Institute. Importantly, priority is given to collaboration with clinical research centres as well as teaching at the Charles University in Prague.

Over the course of its history, the Institute of Physiology has hosted many high profile scientists including for example, Professor Helena Illnerova (President of the Czech Academy of Sciences (2001-2005)) and Professor Bohuslav Ostadal, (President of the International Academy of Cardiovascular Sciences). Since 1991, it also supports its "own" scientific journal: "Physiological Research" with Dr. Jaroslav Kunes currently acting as the Editor in chief. This journal constitutes a valuable "academic forum", as well as providing additional international visibility for the Institute.

Under the Institute's current director (since 2015), Prof. Jan Kopecky, the

Institute hosts 23 Research teams (“Departments”) whose research is supported by 6 service departments. Together, these encompass approximately 400 employees representing around 300 FTEs. 40% of scientists in the Institute are female and in an important step towards fostering a good gender balance, the present head of the Institute council is female (Dr Alena Sumova). The current report is based on an assessment of 14 of the 23 “Departments”.

## **2. Strengths and Opportunities**

1) The main research themes represent a clear strength for the Institute of Physiology. The Institute clearly addresses highly relevant issues for healthcare, notably in the domains of Cardiovascular Medicine and Neurophysiology. Furthermore, the synergistic, multidisciplinary research approach incorporates an attractive mix of both *in vitro* and *in vivo* research. Combined with the strong track record of the Institute in national and international collaborations with other academic and medical research centers this has proven to be a highly effective strategy. Reflecting this successful formula, the Institute has many well-experienced PIs with strong international visibility as well as a clear general high level of motivation and a set of vibrant public engagement activities.

2) In terms of productivity, the Institute has a very good publication record: During the evaluation period the Institute has accumulated 714 publications with a total impact factor of 2314, including 31 papers in journals carrying an impact factor of more than 7, with 3 papers in Nature. The broad range of international collaborations has been supported by the Institute’s involvement in 19 European funding programmes (Marie Curie Reintegration grants, Marie Curie Initial Training Networks, COST and FP projects), one Howard Hughes Medical Institute award as well as 32 bilateral projects. As a consequence of this international activity, more than 50% of PhD graduates from the Institute have travelled abroad to study for their postdocs.

3) A major advantage for the Institute is the current Director, Prof. Jan Kopecky,

who brings strong leadership and who is very much proactive in tackling forthcoming problems. Critically, a very constructive working dialogue and collaboration exists between the Director and the Institute Council. As a consequence, the Institute aims to implement an entirely convincing vision for the future. This entails the pursuit of the original visionary goals by building on the experience of existing scientific teams and where possible, recruiting new talent. In this regard, the management team has implemented an effective recruitment strategy although with some constraints (see Weaknesses and Threats section below). Key to their future strategy is the development of cooperation with other institutions on campus.

### **3. Weaknesses and Threats**

1) One motto that the Institute seems to have adopted is "*E pluribus unum*". While certainly diversity in research activities can be a source of opportunity, too much risks to jeopardize focus, cohesion and synergy. In this regard, several of the smaller "Departments" (or more appropriately, groups) lack critical mass and so represent weak points for achieving the global strategy and vision of the Institute. This tendency to "fragment" research efforts is in part exacerbated by the domestic funding landscape which inevitably encourages the development of smaller scale, shorter duration projects. There is a consequent lack of concerted effort to apply for longer term, more ambitious (e.g. ERC-level) funding and so an impairment of long-term conceptual research. Furthermore, there is room for improvement in the arenas of translational activities and intellectual property rights.

2) One set of problems that is certainly not unique to this Institute, is a general weakness in the age structure. Five or six of the group leaders will be retiring in the relatively near future with still no concrete plans to replace them. Furthermore, there are clear problems to attract and maintain middle career scientists, in large part due to internationally non-competitive salaries and so there is an inevitable "brain drain" effect. These problems are compounded by

funding constraints which for example retard investment in new infrastructure that would be needed to competitively recruit new senior scientists.

#### **4. Recommendations**

The commission was very positively impressed by the progress of the Institute during the evaluation period as well as its plans for the immediate future. However, the commission also identified several key areas where the Institute should focus special attention in the forthcoming period:

1) *Strengthening the links with clinical partners*: The commission appreciated and strongly encouraged the ongoing efforts to recruit clinicians into advisory roles within the Institute as well as recruiting more medical students and engaging them in research involving clinical applications. This approach will be essential to enable all clinically relevant research findings to find the visibility and applications they deserve.

2) *External guidance of research strategy*: The commission sees the establishment of an external advisory board for the Institute as a crucial step towards maintaining a competitive position in relation to similar Institutes outside the Czech Republic. Ideally this board should be comprised of international experts from the domains of research activity within the Institute. Regular meetings to evaluate progress and discuss future directions together with close collaboration with the Director and the Institute Council would provide an invaluable forum to guide the Institute and to ensure it remains internationally competitive.

3) *Strengthening PhD training activities*: Due to the difficulties to attract excellent postdoctoral fellows because of the salaries that are low on an international scale, there is an even greater dependence on training excellent PhD students. For this reason the commission greatly appreciated the efforts to enhance the training of PhD students. Existing activities such as PhD student “Retreats” and the Introductory course are all immensely positive. However, it is imperative that

the Institute continues to foster the identity of this Graduate School to bring it more into line with international Graduate Schools from other countries which have increasingly become the norm for high quality PhD training programmes. The multidisciplinary research and close contacts with clinical-related research makes the Institute an attractive location for PhD students looking for modern career training. However, having a more visible Graduate training programme that would complement their core research activities would greatly enhance the attractiveness of the Institute. It would be beneficial to appoint a high ranking researcher within the Institute to serve as a figure head for these training activities and to coordinate future developments.

4) *Developing local, strategic alliances:* The ability of Institutes on campus to cooperate is immensely important for developing a dynamic and modern teaching strategy, for strengthening cross-discipline research projects and for building a strong national and international visibility. For this reason, the Commission actively encourages the Director and Institute council to continue to identify and to build alliances with other strategically important institutes on campus.

5) *Rationalize the research organization of the Institute:* The choice of the term “Department” was confusing for the commission, given the implication of much larger research structures which would be commonly found in other international institutes. In essence, the Departments are better defined as “Groups” or “Teams”. The commission actively encourages the Director and Institute Council (with hopefully help from an external scientific advisory board) to examine the existing structure with diverse and in many cases, small groups, to identify areas of critical mass and new potential synergies. Such an exercise would be one important step to remedy “fragmentation” fostered by funding via a multitude of small domestic grants which in many ways impairs long term conceptual research and so somewhat unjustly limits the impact of the work of the Institute in the international arena.



## **5. Detailed evaluations**

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

The commission concludes that the results of the Institute are overall very good, in part excellent. In some collaborative projects, the Institute has a leading role, in all others it provides essential contributions.

### *Declaration on the involvement of students in research*

The commission considers the involvement of student very good and very well organized. However, strengthening complementary Graduate School activities would represent a significant boost to this area.

### *Declaration on societal relevance*

The commission considers the societal relevance high, given the Institute's core research focus.

### *Declaration on the position in the international and national context*

The commission concludes that the Institute is competitive at the international level. Nationally the Institute occupies a leading position.

### *Declaration on the vitality and sustainability*

The commission considers the vitality and sustainability of the Institute good, although some excellent projects are underfunded. More money should be available to provide some targeted supplementary support and thereby to foster promising new groups.

### *Declaration on the strategy and plans for the future*

The commission concludes that a convincing, clear strategy was presented that is shared by the director and the Council.

## **B. Evaluation of the individual teams**

### **Evaluation of the Team No. 1: Experimental Hypertension**

#### **1. Introduction**

The Department of Experimental Hypertension is a group lead by Josef Zicha. The group currently consists of 5 senior and 5 junior scientists as well as two technicians and two students. It is overall a medium sized group.

Their main scientific focus lies in blood pressure control, the role of calcium influx and sensitization in arterial resistance, and its relationship to the RhoA/Rho kinase signaling. They use animal models of either genetic (e.g. SH rats) or pharmacological (e.g. chronic NOX inhibition) induction of hypertension.

#### **2. Strengths and Opportunities**

The commission identified the following strengths and opportunities:

(1) The group has a reasonable publication record during the evaluation period in mid-range journals.

(2) Hypertension represents a very important clinical problem with many areas needing further research activity.

(3) The group has managed to recruit some mid-ranking scientists in order to improve the overall age structure.

#### **3. Weaknesses and Threats**

The commission identified the following weaknesses and threats:

(1) It was surprising that the group leader resisted the possibility to apply for EU-funded collaborative projects.

(2) The overall methodological spectrum of the group is rather narrow and traditional which limits the potential for future scientific development.

(3) Research on neuropeptides represents an area of high scientific activity which will impose a very strong international competition on the group.

(4) Retirement of the group leader without a clear succession plan so far, poses a major threat to the group's future perspectives.

#### **4. Recommendations**

The expertise in this group would possibly be better suited in a merger with another group, e.g. Developmental Cardiology.

#### **5. Detailed evaluations**

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

The commission concludes that the results of the group are overall good, in part very good.

*Declaration on the involvement of students in research*

The involvement of students in research is low.

*Declaration on societal relevance*

Societal relevance of the research is very high.

*Declaration on the position in the international and national context*

The commission concludes that the group is nationally competitive and internationally visible.

*Declaration on the vitality and sustainability*

Vitality and sustainability of the group are secure, with the limitations outlined under 'Weaknesses and Threats'.

### *Declaration on the strategy and plans for the future*

The commission feels that strategy and plans for the future are limited by the scope of the methodology and the narrow scientific orientation.

## **Evaluation of the Team No. 5: Adipose Tissue Biology**

### **1. Introduction**

The Department consists of six research scientists. It is led by the Director of the Institute, Prof. Jan Kopecky. The Department also comprises, currently, 5 PhD students and 3 MSc students; 7 PhD students have completed their theses within the evaluation period between 2010-14 and the majority have gone on to academic research positions or to work with local biotech companies. Four of the research scientists have experience of working outside the Czech Republic, in the US, in the Netherlands and in France. Prof. Kopecky, age 64, is the most senior member of the Department. Clear strategies for succession have been identified which will allow Kopecky to develop the clinical trials emerging out of the current work of the Department.

The Department investigates the physiological regulators of metabolism and their disorders in obesity. Several of these disorders are clustered in the so-called metabolic syndrome (dyslipidemia, impaired glucose homeostasis and hypertension) and lead to severe diseases (including type 2 diabetes and cardiovascular disorders) which are major concerns for the health care systems in the developed world.

A section of the Department is concerned with the possible use of *n*-3 fatty acids from fish (**omega-3**), eicosapentaenoic (**EPA**) and docosahexaenoic (**DHA**) acids, in the prevention and treatment the diseases associated with obesity. Experimental findings from studies in mice are complemented by mechanistic studies *in vitro*. Some of these studies have been explored, and have resulted in

high impact papers; they are being explored in clinical studies, in conjunction with collaborations with industrial and biotech partners in Norway (in particular Pronova a.s., EPACX a.s. and Olympic Seafood a.s.) These steps are part of a strategy for effective translational research. Some results from human diabetic patients are already in hand for publication in *Nutrition and Metabolism*.

## **2. Strengths and Opportunities**

(1) The commission was impressed by the concept of the 'healthy white adipocyte'. This concept is a fundamental idea how to prevent the adverse consequences of obesity by altering the metabolism of white adipocytes. The work of the Department demonstrated an improvement of triacylglycerol levels by omega-3 fatty acids and by anti-diabetic drugs in mouse models, leading on to clear translational work in clinical trials. The work thus presents an opportunity for validation.

(2) The commission was also impressed by strong internal collaborations between the Department and other departments of the Institute. It was noted that the Department has published many high impact papers and that there has been excellent international experience for many group members. The commission also noted that the Department has a very clear and focused research plan, employing unique methodology to study the pathways. It was also noted that the Department has strong collaborative links with and financial support from industry.

(3) The commission was impressed by a clear plan for succession of the current head, Prof. Kopecky, with the opportunity to develop clinical trials. There are thus clear plans to incorporate translational medicine. It was also impressed that the Department holds two FP7 projects grants (EU FP7 *BIOCLAIMS* and EU FP7 *DIABAT*) on both of which Prof. Kopecky was co-PI.

### **3. Weaknesses and Threats**

The commission could not identify any clear weaknesses

### **4. Recommendations**

The commission was enthusiastic about the work currently pursued and would encourage the Department to keep going in the positive direction!!

### **5. Detailed evaluations**

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

The commission concluded that both the quality of the results and the Department's share in their acquisition was overall very good, in part excellent.

#### *Declaration on the involvement of students in research*

The commission concluded that the involvement of students in research was very good.

#### *Declaration on societal relevance*

The societal relevance of the Department's work is considered high by the commission.

#### *Declaration on the position in the international and national context*

The commission concluded that the Department is internationally competitive, and that it is leading in the national context.

#### *Declaration on the vitality and sustainability*

The commission concluded that the Department shows high vitality and a clear and realistic vision for the future. Thus, sustainability is considered high by the commission.

#### *Declaration on the strategy and plans for the future*

The commission concluded that the strategy and plans for the future were realistic and clear.

## **Evaluation of Team No. 7: Biomaterials and Tissue Engineering**

### **1. Introduction**

The Department currently consists of 6 research scientists and is headed by Associate Professor Lucie Bačáková. The total includes two senior scientists (age > 65 years), but there are 3 junior scientists and 4 postdoctoral fellows. The Department currently has 8 PhD students and 3 MSc students working there. The age balance of the Department is relatively favourable.

The Department has a large number of collaborations both within CAS and with institutes, universities, hospitals, and SMOs in the Czech Republic; there are also links to a number of Universities in the EU and in the US (U Penn) and Australia (U Sydney) which have involved visits and/or exchanges with some Department staff. Senior members of the Department are significantly engaged with the University, giving lectures and supervision of undergraduate and graduate students.

The main thrust of the Department is translational. The main themes are directed towards

- a) Improving currently-used synthetic tissue replacements (mainly vascular and bone replacements) by introducing cell and other biological components. The work has involved chemically modifying adhesive surfaces to ensure good bonding to cell ligands, of particular importance for ensuring that endothelial cells bond to host tissues.
- b) Construction of new tissue replacements based on synthetic and cellular materials. This direction is divided into a number of project ranging from redesign of joint replacement surfaces, bioartificial bone (in collaboration with a CR biotech company) and skin tissue engineering.
- c) Several subsidiary projects such as a perivascular drug delivery system (Fiklova et al. Int J Pharmaceut 404, 94-101 2011) and a new development in bioimaging.

In order to achieve its goals, the Department works extensively with techniques that identify molecular mechanisms of cell behaviour with respect to adhesion, growth, differentiation, phenotypic maturation, viability, metabolic activity, potential damage and immune activation of cells. The Department is well equipped with tissue culture facilities as well as resources for microscopy and time lapse photography, all offering resources for other groups interested in tissue applications of biomaterials.

The work of the Department has had publications in high impact journals. In particular there have been high impact publications on the design of cell adhesive materials by Dr Bacakova et al (Biotechnology Adv. 29, 739-767 (2011)) and on the uses of nanotube modified surfaces for bone cell growth (Stankova et al, Carbon 67:578-91 (2014)). There has also been interest in the Department in subendothelial extracellular matrix proteins and the nature of laminar shear stress (Chlupac et al., Tissue Eng A 20:2253-64 (2014)).

## **2. Strengths and Opportunities**

The commission noted that the Department holds a number of Czech patents and that these are related to the fields of bone and vascular repair, which are important fields for clinical health. The commission recognized that published output of the Department is very well cited and that the work of the Department is strongly interdisciplinary. Biomaterials represent a very attractive topic for translational application and research. The development of nano-diamond related projects seems promising and could be enhanced.

## **3. Weaknesses and Threats**

There is not a clear vision for an independent roadmap for the future. The commission was concerned that effort was being too easily driven by the service position occupied by the Department and research, potentially, was too easily redirected by external requests for biological assays. Tissue engineering is one of the more risky fields, precisely because of its potential for translation and it is



therefore very competitive internationally. The commission concluded that there appeared to be many different approaches being pursued, only some of which had competitive translational potential.

#### **4. Recommendations**

The commission concluded that the Department should clearly prioritize its projects. All approaches mentioned need huge systematic analysis to make them credible and translatable but this type of research is not possible within the current funding profile of the Department, which is driven by relatively short limited research “episodes”. This group, based in a basic research institution has adopted a strategy of “playing” and doing critical preliminary research for companies. Moving forwards, it should take ideas and focus on those that are already close to applications.

The commission also felt that there should be further attempts to develop expertise in the Department over a wider and more complete spectrum of methodology. There is currently a focus on cell culture. For projects involving e.g. in-vivo work on vascular replacement, it is necessary to selectively foster collaborations with clinical as well as with experimental medicine. The Department appeared to be open to all collaborations, which is not necessarily the best strategy to acquire grant money. The commission also recommends that steps should be taken to foster links between the Department and Biotech companies in order to enhance its potential in pre-clinical research.

#### **5. Detailed evaluations**

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

The commission concluded that results of the Department were overall very good.

##### *Declaration on the involvement of students in research*

The commission concluded that the involvement of students in the research of the Department was very good.

*Declaration on societal relevance*

The commission concluded that the societal relevance of the work in the Department is high.

*Declaration on the position in the international and national context*

The commission concludes that the Department is internationally very visible. In the national context, it occupies a leading role.

*Declaration on the vitality and sustainability*

The commission concludes that the vitality and sustainability of the Department is good.

*Declaration on the strategy and plans for the future*

The commission recommends that the Department revises its strategy with regard to the points described above, and that it should prioritize its plans for the future.

## **Evaluation of Team Nr. 8: Cellular and Molecular Neuroendocrinology**

### **1. Introduction**

Professor Zemkova heads a small but productive and well-focused Department, consisting of herself, 3 junior research workers, a postdoctoral fellow, a retired (non-experimental) worker, 2 PhD students and 2 Technicians. The age-spectrum ranges from 25-35 (2 staff), 40-45 (2 staff) up to 60-65(1).

The main interest of the group are the electrical events, ion channels and receptors that control secretion from pituitary and hypothalamic neuroendocrine cells. Dr. Zemkova herself also has a special interest in ATP-gated P2X cation channels.

During this review period they published 24 citable papers; of 11 assessed, 7 were rated internationally excellent or above, and one of which was considered world-leading. Work of note concerns cholinergic signalling in pituitary gonadotrophs (Zemkova et al., 2013: *Endocrinology*, 154,421-433), adrenergic signalling in pinealocytes in relation to melatonin secretion (Zemkova et al, 2011: *Endocrinology*, 152, 3842-51), and regulation of inhibitory transmission by ATP in cells of the suprachiasmatic nucleus (Bhattacharya et al, 2013: *J Neurosci.*, 33,8035-44), plus a substantial body of work relating structure and function of P2X receptors by site-directed mutagenesis combined with electrophysiology and molecular modelling led by Zemkova and Stanko Stojilkovic at NIH (USA).

Members of the Department have maintained productive collaborations with several labs outside the Czech Republic including the National Institute of Child Health and Human Development, NIH (USA), A. I. Virtanen Institute, Kuopio, Finland, McGill University, Montreal, Quebec, Canada, and University College London.

## **2. Strengths and Opportunities**

The commission identified the following strengths and opportunities:

- (1) High quality, well-focused and internationally-competitive research
- (2) Outward-looking, strong international connections
- (3) State-of-the-art technology (electrophysiology, transgenics, site-directed mutation, homology modeling, molecular dynamic simulation)
- (4) Interesting & feasible short-term future projects (mechanism of CRH release from corticotrophs, mechanism of agonist-dependent dilatation of P2X7 channel pore).
- (5) One interesting long-term project about microRNA regulation of purinergic signaling in the hypothalamus.

### **3. Weaknesses and Threats**

The commission identified the following weaknesses and threats:

- (1) The small number of research staff could compromise the overall potential and flexibility of the Department.
- (2) Very few graduate students are involved in the research; for reasons that are not apparent.
- (3) The proposed long-term project about pore-dilation in P2X receptors may need revision in the light of new findings that the change in apparent pore permeability may result (at least partly) from changes in transmembrane ion concentration gradients [see Nat. Neurosci., 2015:18, 1534-5 and 1577-83].
- (4) The retirement of Professor Zemkova will leave a major gap. No plans were presented for a successor.

### **4. Recommendations**

The commission recommends to

- (1) consider the possibility of a merger with another group which share common interests and technologies,
- (2) seek recruitment of competent postdocs with strong credentials and a track record in appropriate areas,
- (3) increase participation of graduate student in the research activities.

### **5. Detailed evaluations**

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

The commission concluded that the results of the group are excellent.

*Declaration on the involvement of students in research*

The involvement of students in the research was considered weak by the commission; only 30% of them were authors or co-authors of papers published during the evaluation period.

#### *Declaration on societal relevance*

The research of the Department was considered of societal relevance by the commission.

#### *Declaration on the position in the international and national context*

The Department is internationally competitive, and among the leaders in the national context.

#### *Declaration on the vitality and sustainability*

Vitality and sustainability are excellent at present but may be difficult to sustain after the next 1-2 years.

#### *Declaration on the strategy and plans for the future*

The commission concludes that strategy and plans for the future are good in the short term. However, additional long-term strategies in neuroendocrinology may be needed. At present, all future long-term proposals concern ATP and P2X receptors which is a little narrow (and have not, as yet, led to promising lines of therapy or translational applications for any neural or endocrine disorders).

### **Evaluation of Team Nr. 9: Cellular Neurophysiology**

#### **1. Introduction**

The team is led by Ladislav Vyklický and consists of 11 research workers (5 senior scientists, 2 junior scientists, 2 postdoctoral fellows, 1 research development assistant, 1 Emeritus) plus (currently) 9 PhD students. The main research emphasis is on the physiology & pharmacology of ion channels (mainly NMDA receptors and TRP channels). The Department is well respected internationally and with high quality publications in major mainstream journals such as *J. Physiol*, *J Biol Chem*, *Neuropharmacology* and *Br. J. Pharmacol.* and with collaborative papers in *Neuron* and *EMBO J.* 75% (12/16) of the assessed papers were placed in classes 1 and 2 (world-leading or internationally excellent).

This is a notably outward-looking Department. Professor Vyklycky himself is well recognized and respected internationally, in part through having worked at NIH Bethesda, USA, and MPI Heidelberg, and has a creditable H-index of 24. He will be approaching retirement within the next few years. Overall, the Department has good connections with non-CR labs. Professor Vyklycky's equally well-known predecessor, Professor Vyskocil (now Emeritus), has worked in Kazan University and the Sechenov Institute in Russia and UCSF, USA, and several other staff members have also spent time in "foreign" labs including: NIH USA; LMB Cambridge UK; Manchester University, UK, Washington & Northwestern Universities and UCSF, USA. The Department also has numerous international collaborations. These include participation in a 6<sup>th</sup> EU Framework programme on characterization of transmitter-gated ion channels in drug discovery, and specific collaborations with members of the Central Lancashire University, UK; Washington University, St Louis, USA; Seoul National Medical University, S.Korea; MRC LMB, Cambridge, UK; Max Perutz Lab, University Vienna, Austria; and Institute of Physiology, University Erlangen, Germany. Members of the Department play a full part in student instruction and supervision, and in general scientific communication, facilitation and administration outside the CAS itself.

## **2. Strengths and Opportunities**

The commission identified the following strengths and weaknesses:

- (1) The research of the group is of very high quality, and comparable to that in many major labs outside the Czech Republic. This is the strongest group of the Institute!
- (2) The Department is outward looking (see above) and hence well-aware of international standards, and it is competitive therewith.
- (3) The Department has made some notable advances in understanding ion channel physiology, such as endogenous neurosteroid regulation and other properties of NMDA-type ionotropic glutamate receptor channels, determinants of

ionotropic glutamate receptor trafficking, and the molecular bases for the complex gating of some transient receptor potential (TRP) cation channels.

(4) Future plans based on these themes look very promising and should yield important results. An ambitious and exciting project is the suggested link between genetic variations in NMDAR complexes and schizophrenia.

(5) The abundance of external collaborations speaks well of the international strength of the Department. Its strong instrumental infrastructure and modern technological approaches should also be attractive for PhD students.

(6) The overall healthy age-spectrum (with 17/22 staff below 40) speaks well for the future (see further in section 3).

(7) The Department pays attention to translational possibilities of its results; 6 patents have been filed.

### **3. Weaknesses and Threats**

The future retirement of Professor Vyklicky and the difficulty to appoint a young successor (Dr. Vachlova being 58) could cause problems (but also could offer opportunities).

### **4. Recommendations**

The commission recommends a concerted drive to recruit high quality postdocs as future independent team leaders, with some flexibility regarding new versus continuing areas of research.

### **5. Detailed evaluations**

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

The commission concludes that the results of the team are excellent.

*Declaration on the involvement of students in research*

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

*Declaration on societal relevance*

The societal relevance of the research is appropriate.

*Declaration on the position in the international and national context*

The Department is internationally competitive, in parts among the leaders in the field. The Department is leading in the national context.

*Declaration on the vitality and sustainability*

Vitality and sustainability of the Department are high, provided a successful recruitment of competent scientists.

*Declaration on the strategy and plans for the future*

Strategy and plans for the future were clearly presented and fully convincing.

**Evaluation of Team Nr. 10: Epithelial Physiology**

**1. Introduction**

This is a small Department lead by Dr. Jiri Pacha. The Department comprises two junior scientists and a postdoctoral fellow. One PhD student and two diploma students are currently working in the Department, and 4 PhD theses have been successfully defended within the evaluation period 2010-14. Two of these have gone abroad to work (Sweden and Switzerland) and are counted amongst the present staff, while one has returned to clinical medicine.

There are three main topics of research within the Department. The topics overlap, and are intended to provide insights into inflammatory and neoplastic bowel diseases:

The first theme is the study of local metabolism of glucocorticoids and their role in inflammation, particularly concentrating on the regulation of the enzyme 11HSD1 in the conversion of cortisone to cortisol. Both rat models of colitis and



human patients have been studied; the way in which stress can amplify glucocorticoid signalling has resulted in publications (e.g. Vodicka et al, PLoS One 2014). The expression of pro-proliferative and antiapoptotic genes in colitis-associated neoplasia and the local metabolism of glucocorticoids as a possible associate of inflammatory bowel disease is a central concern of the Department and there is an ongoing interest in determining whether changes in glucocorticoid metabolism are part of the feedback regulation of hypothalamus-pituitary-adrenal (HPA) axis via limbic structures, PVN, pituitary and adrenal glands.

A second inter-related theme is understanding whether genes encoding transporters of intestinal absorption and secretion are regulated by the circadian clock. One finding reported during 2010-14 is that the rhythmicity of circadian clock is changed during tumorigenesis, with the circadian expression patterns of *Per2* and *Bmal1* being almost abolished in primary tumours (Sotak et al, In J Cancer 132:1032, 2012).

The third topic of the Department's work is to measure the effect of temporal regulation on intestinal transport. Work on  $\text{Na}^+$  transport in the rat colon using electrophysiological methods has shown that the time of day directly affects transport rates (Sotak et al, Am J Physiol, 301:G1066 2011) whereas more recent work has been directed to the study of ABC transporters.

## **2. Strengths and Opportunities**

The commission considers the projects very interesting. The results are of potential clinical importance for inflammatory bowel disease, a major human health concern. The commission believes that there are opportunities for mechanistic explanations for how the clock regulates transport pathways; this is known in other tissues, where transport capacity changes, and not just in the protein levels. Furthermore, there are opportunities to study how the integration of activity could also be clock controlled, for example in digestive enzymes and by the anticipation of food. Some clock genes are very tissue specific: it is an important issue to identify which clock gene elements are critical in the GI system.

### **3. Weaknesses and Threats**

- (1) The commission feels that the Department is probably too small to successfully pursue all the projects proposed for the next years. There appear to be just too many diverse projects in three large, very competitive fields (inflammatory bowel disease, carcinogenesis and clock genes, gut microbiota).
- (2) The commission's opinion was that the microbiome project might be too competitive for the group to exert an international impact.

### **4. Recommendations**

The commission strongly recommends that it is important to incorporate the proposed projects into a multidisciplinary collaborative effort. Some of the projects are already carried out in collaboration with the Department of Neurohumoral Regulations of the Institute of Physiology, and this connection should be strongly reinforced, particularly for the clock project.

The commission questioned the future plans which proposed an investigation of circadian rhythms on tumorigenesis. In his response, Dr. Pacha proposed to disturb the circadian rhythm in a rat model of chemically induced cancer, and then to analyze healthy and tumor tissue. The commission felt that it would be difficult to demonstrate causality of the circadian clock for tumorigenesis and suggested to consider mouse models with a high rate of spontaneous neoplasms, and cross them with a clock mutant (e.g. *per2* mutant) in order to test whether the progeny exhibits a higher incidence of neoplasm formation.

### **5. Detailed evaluations**

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

The commission concluded that the quality of the results and the Department's role in their acquisition was good.

#### *Declaration on the involvement of students in research*

The commission concluded that the involvement of students was very good.

*Declaration on societal relevance*

The societal relevance of the Department's work is considered high by the commission.

*Declaration on the position in the international and national context*

The commission concluded that the Department is visible in the field both in the national and international context.

*Declaration on the vitality and sustainability*

The commission was concerned that the Department lacks a critical size; with only two junior scientists its position could be risky.

*Declaration on the strategy and plans for the future*

The commission concluded that the plans for the future were scientifically sound, but far too broad for the group size.

## **Evaluation of Team No. 11: Functional Morphology**

### **1. Introduction**

This team headed by Dr. Jiri Palecek consists of 2 senior scientists, 1 junior scientist, 1 post doctoral fellow, 7 PhD, 4 MSc and 4 BSc students. Strikingly, its research is split between two quite different topics. The first, under the direction of Jiri Palecek is focused on the mechanisms underlying neuropathic pain, while the second is directed by the second senior scientist Dr. Tomas Soukup, and investigates the effects of hormones and agents on the expression of muscle proteins and on the fibre type. During the evaluation period this team has produced a total of 31 outputs with roughly 1/3 from the pain subgroup group and 2/3 from the muscle protein. Of these, 6 were evaluated and 2 were categorised as Internationally excellent, 3 Internationally recognised and 1 as nationally recognised.

The work of the pain section of this team has in particular addressed the function of the spinal cord TRPV1 receptors in the context of nociceptive transmission and pathological pain. They have developed an experimental approach using a combination of electrophysiology, immunohistochemistry, molecular genetic and behavioural analysis. Notably, they have extensively used patch clamping to measure electrical activity of superficial dorsal horn neurons in acute spinal cord slices. The team has explored the contribution of neuroinflammatory cytokines such as TNFa as well as chemokines e.g. CCL2 to increasing the sensitivity of the TRPV1 receptor to activation.

The muscle section has focused on the role of thyroid hormones and omega 3 polyunsaturated fatty acid in cardiac and skeletal muscle physiology in particular in the definition of fast and slow fiber types. This work relies on the use of hyper and hypothyroid rodent models as well as muscle grafting models combined with molecular genetics methodology.

## **2. Strengths and Opportunities**

The commission identified the following strengths and opportunities:

- (1) The team is engaged in strong international connections and collaborations.
- (2) Research topics are highly relevant and timely.
- (3) The commission views the expertise of the senior scientists in state-of the-art methodology as a particular strength.

## **3. Weaknesses and Threats**

The commission identified the following weaknesses and threats:

- (1) The partition of this group into two very different research areas with no apparent interaction tends to dilute their impact.
- (2) The commission missed a perspective for clinical application (e.g. to develop a novel strategy to treat diabetic neuropathy).

#### **4. Recommendations**

The commission suggests a restructuring/reallocation of the group so that the two different parts are linked up with more suitable partners.

#### **5. Detailed evaluations**

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

The commission concludes that the results of the team are overall good, in some parts very good.

##### *Declaration on the involvement of students in research*

The involvement of students in the research is considered adequate by the commission.

##### *Declaration on societal relevance*

The societal relevance of the research is considered high by the commission.

##### *Declaration on the position in the international and national context*

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

##### *Declaration on the vitality and sustainability*

Vitality and sustainability appear adequate, limited by the heterogeneity of the research aims as described above.

##### *Declaration on the strategy and plans for the future*

The commission concludes that the research strategy and plans were overall reasonable and sound but missed a convincing clinical translation element. In addition, the combination of the two separate directions in a single team was not entirely logical.

## **Evaluation of Team Nr. 13: Cardiovascular Morphogenesis**

### **1. Introduction**

The Department of Cardiovascular Morphogenesis is a relatively newly created (since 2009) small Department with David Sedmera as Department head. In addition to the PI, the group comprises 2 junior scientists, currently 4 PhD students and one technician. Their scientific focus is on the regulation of embryonic cardiac development, especially the molecular mechanisms of the formation of the conduction system. They use novel methods and overall presented a very dynamic team structure.

### **2. Strengths and Opportunities**

(1) The group gave an enthusiastic and very knowledgeable impression, employing innovative methodology and a convincing strategy for further scientific advance in an exciting research area. The breadth of the group's activities given its size impressed the commission.

(2) The group presented a strong future potential, with many foreign-trained student, good internal cooperation and many foreign collaborators.

(3) In addition, many contacts to clinical research groups have been presented and bear great opportunity for translation of the findings.

### **3. Weaknesses and Threats**

The main threat for this group is its size – it might be too small for the very ambitious goals.

### **4. Recommendations**

The commission recommends to further support this group in order to bring the strong ideas into action.

## **5. Detailed evaluations**

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

The commission concludes that the results of the group were overall very good.

### *Declaration on the involvement of students in research*

The involvement of students in the research is considered very good by the commission.

### *Declaration on societal relevance*

The societal relevance of the research is high.

### *Declaration on the position in the international and national context*

The commission concludes that the group is internationally visible, and that it has a pioneering role in the national context.

### *Declaration on the vitality and sustainability*

The commission concludes that vitality and sustainability of the groups are limited by its small size. The group deserves extra support from the Institute to reach a critical mass.

### *Declaration on the strategy and plans for the future*

The presented research concept was sound and convincing but in part too broad and ambitious given the small size of the group.

## **Evaluation of Team No. 15: Neurochemistry**

### **1. Introduction**

The Neurochemistry team is a small Department comprising currently 4 full-time researchers (plus 2 on maternity leave) plus 3 PhD students. Its research aim is the biochemical analysis of cholinergic transmission and of muscarinic

acetylcholine receptor pharmacology in the brain. In this it inherits the tradition inaugurated by the internationally respected neurochemist Professor Stan Tucek (1932-2002) who headed the Department until 1997. The current Head, Professor Dolezal, worked with Tucek and is now aged 62.

One important part of the Department's work follows a concept partly developed by Tucek, namely that one can obtain higher drug selectivity (both inhibition and activation or enhancement) among the 5 muscarinic receptor subtypes M1 to M5 with compounds directed at allosteric binding sites rather than orthosteric sites. This is now a major direction of pharmaceutical drug development. Professor Dolezal and his team have now identified a novel allosteric binding site for methoctramine on the M2 muscarinic receptor (Jakubík et al., *Mol Pharmacol*, 86:180, 2014). They have also done important quantitative work concerning the kinetics of signalling between the agonist-induced activation of muscarinic receptors and cognate GDP/GTP-binding proteins (Jakubik et al., *Br J Pharmacol* 162:1029, 2010; Jakubik et al., *PLoS One* 6:e27732, 2011) which, inter alia, indicates G protein-dependent receptor-G protein precoupling (a much-discussed question since it affects the kinetics of the downstream signalling process). Another interesting finding is that the "Alzheimer protein" amyloid  $\beta$ 1-42 directly and specifically attenuates M1 receptor – G protein interaction in isolated membranes (Janickova et al, 2013: *Neuropharmacology*, 67,272-283), which accords with their previous observation of disrupted muscarinic signalling in the brains of adult but not immature transgenic Abeta1-42 Alzheimer model mice. Their work is largely done through careful radioreceptor binding assays plus GTPase and second messenger assays, coupled with site-directed receptor or G protein mutation and kinetic or molecular modelling. They also propose to introduce optical techniques such as FRET. As indicated above, much of their work is published in first-rate international peer-reviewed journals (8/13 assessed in group 1 or 1\*), though oddly most papers so assessed have only been rated group 3, not 2, for reasons that are unclear.

For the future, in addition to developments of the above lines of work, they



propose to study further factors that might cause or ameliorate Alzheimer's disease including the role of ApoE and dietary lipids (the latter as an extension of a project with Danone Research indicating that such lipids can enhance M1 receptor – signalling in isolated cells (Savelkoul et al., J Neurochem 120:631, 2012). They are also involved with 9 other labs in a project to test effect of diet lipids on neuronal and cognitive performance in aging and are applying to EU Horizon 2020 program for a trial to assess whether nutritional changes can prevent functional decline in aging.

## **2. Strengths and Opportunities**

- (1) The Department comprises internationally respected scientists with broad and proven expertise in neurochemical techniques for the study of ligand-receptor interaction and signaling.
- (2) Well-focused research themes leading to publications in strong international peer-reviewed journals.
- (3) Good international collaborations with the University of Minnesota Medical School and Barry University, Florida, and with other labs in the Czech Republic.
- (4) Interesting (though somewhat speculative) future plans for research in areas with potentially high societal impact, as well as feasible studies at the cell and molecular level.
- (5) Employment of optical techniques in collaboration with the CR Institute of Physical Chemistry.

## **3. Weaknesses and Threats**

- (1) The Department is relatively small. Given that 2 scientists are currently on maternity leave, personnel shortage limits the possibility of taking on new, competitive projects.
- (2) The Department has a relatively narrow research topic focus presently (constrained by the limited number of researchers).
- (3) Current methods assess mainly steady-state equilibrium. The methodology would gain by more dynamic optical approaches (see, e.g., work by B. Hille et al,

J.Gen.Physiol.,141,521 & 537) .

(4) There is no clinical or translational collaborations. This weakness may limit funding opportunities.

(5) Prof. Dolezal is expected to retire within 5 years.

#### **4. Recommendations**

(1) The succession of the team leader and the future research direction of the Department should be planned, preferably with an external advisory board.

(2) In view of increasing interest in aging, perhaps some development of collaboration with the Dept. of Neurophysiology of Memory might constitute a mutually beneficial extension for both departments.

(3) Consider enhanced interaction and collaboration with investigators from industry and clinical research.

#### **5. Detailed evaluations**

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

The commission concludes that the results of the Department are overall very good.

##### *Declaration on the involvement of students in research*

The involvement of students in the research is considered limited but adequate by the commission.

##### *Declaration on societal relevance*

The societal relevance of the research is considered limited but increasing by the commission.

##### *Declaration on the position in the international and national context*

The commission concludes that the group is visible in the international as well as the national context.

#### *Declaration on the vitality and sustainability*

Vitality and sustainability of the team are considered good by the commission, with the limitations described above (small group, no plans for succession of Dept. head).

#### *Declaration on the strategy and plans for the future*

Strategy and plans for the future are considered sound and interesting by the commission. However, the commission also identified the above-described weaknesses, and some aspects (e.g. diet & aging) are a little speculative.

### **Evaluation of Team No. 16: Neurophysiology of Memory**

#### **1. Introduction**

Since 2010, Professor Ales Stuchlik has headed this relatively large and productive Department, consisting of himself, 4 other senior scientists, 4 junior scientists and Postdocs, 12 PhD students and 5 lab assistants. The age-spectrum of the group as of December 2014 ranged from 30-35 (1 staff), 35-40 (3 staff) up to 40-45 (4 staff). The research focus of this team is to elucidate the physiology and pathophysiology of memory traces, representations and cognitive functions in dynamic and moving environments. In particular, this team has demonstrated considerable expertise in the testing of behavioural and cognitive functions in laboratory animals. This work represents very much the continuation of a legacy provided by the pioneering work of Jan Bures.

During the evaluation period there were 77 publications of which 16 were further graded in Phase I of the current evaluation. Of these, 3 were classified as "World leading", 2 as "internationally excellent" and 11 were "recognised internationally". Consistently, the group has targeted high ranking journals such as *PNAS*, *Hippocampus*, *Frontiers in Behavioural Neuroscience*, *Behavioural Brain Research*, *Neurobiology of Learning and Memory* and *Neuropsychopharmacology*.

These publications charted work in four main areas: 1) The spatial navigation of rodent models in dynamic environments and their behavioural flexibility. Notably this included studies that first implicated the dorsal hippocampus in avoidance of moving but not stationary objects (Telensky et al., PNAS 108, 5414, 2011) and also validated the use of virtual reality to present spatial stimuli to rats. 2) The development of animal models for neuropsychiatric diseases which included an international collaboration to evaluate a transgenic rat model showing reduced Nogo-A expression as a model for schizophrenia (Petrasek et al, Front. Behav. Neurosci., 2014 and Neurobiology of Learning and Memory, 2014). 3) Documenting spatial navigation and cognitive defects in Alzheimer's disease patients by developing, for example, the Blue Velvet Arena test (Nedelska et al., PNAS, 109, 2590, 2012) and 4) The use of animal models to assess new neuropsychiatric therapeutics based on steroidal compounds (e.g. Holubova et al., Front. Behav. Neurosci. 8, 130, 2014) which also was a source of 4 patents for the group. These activities have led to the involvement of the team in many national and international collaborations.

## **2. Strengths and Opportunities**

- (1) The team has strong track record of publications, some in high-impact journals.
- (2) The team is young, comprises several experienced PIs and has the critical mass to take on competitive projects.
- (3) There are many opportunities for translational activities. The group actively seeks the commercial exploitation of results and has obtained several patents.
- (4) The team cooperates with the business sector.

## **3. Weaknesses and Threats**

- (1) The future plans appear too diverse, in part even fragmented.
- (2) The experimental models that the team is developing are at risk of being restricted by the animal's rights legislation.

(3) International visibility as judged from the numbers of citations should be higher.

(4) The group appears to be of limited attraction for foreign researchers.

#### **4. Recommendations**

(1) Enhance international collaborations.

(2) Follow a publication strategy that can enhance the international visibility and acknowledgement of the results.

(3) Establish links with clinical research that provide input into the preclinical research, and facilitate translation of the results.

(4) Recruit more international researchers to the group.

#### **5. Detailed evaluations**

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

The commission concludes that the results of the team were very good, in part excellent.

##### *Declaration on the involvement of students in research*

The involvement of students in the research was considered excellent by the commission.

##### *Declaration on societal relevance*

The societal relevance of the research was considered high by the commission, in particular with regard to neurodegenerative diseases and drug development.

##### *Declaration on the position in the international and national context*

The group is leading nationally, and is visible in the international context.

##### *Declaration on the vitality and sustainability*

Vitality and sustainability are considered to be currently excellent by the commission.

### *Declaration on the strategy and plans for the future*

The commission concludes that strategy and plans for the future were very good, in part excellent, but have a tendency to be too diverse.

## **Evaluation of Team Nr. 17: Neurohumoral Regulations**

### **1. Introduction**

Dr. Alena Sumová heads a small but very active, focused and well-balanced department, currently consisting of herself, 1 junior scientist, 1 Emeritus, 3 PhD students, 2 MSc students, 2 BSc students, 1 research and 2 laboratory assistants. Except for the PI and the emeritus, this is a “young” team with an age distribution between 25 and 40. The major research theme is the biology of Circadian Rhythms. As such, it carries forward a long tradition established by Prof. Helena Illnerová over 40 years ago for the study of how light and photoperiod effect the regulation of rhythmic melatonin production by clock via the pineal gland. More specifically, they have addressed three key issues: the photic regulation, ontogeny and physiological function of the Circadian Clock. They have made many important contributions to our understanding of the effects of photoperiod and light in setting the clock as well as the ontogeny of the clock mechanism and maternal effects on the developing fetal clock in rodents, (for which they have been notable pioneers). In addition, this team is currently exploring links between the clock, colorectal cancer, hypertension and neuropsychiatric diseases. The team tackles these issues by applying a broad repertoire of molecular biology, cell culture, advanced microscopy, pharmacological and behavioural analysis methodology in the context of various mouse and rat genetic models. The Sumová group is also now pursuing projects which directly address circadian clock function in humans. This has involved, for example, the development and application of various non-invasive tests for circadian clock function. The group has a broad international visibility and has

successfully published high quality results. During the evaluation period, 25 publications were reported. Of the 5 evaluated, 4 were classified as internationally excellent or internationally recognised.

Doctor Sumova is a highly respected, senior figure of the international circadian clock research field. This stems from her own training abroad in MRC, Cambridge as well as her collaborations involving exchange of personnel with MRC Cambridge UK, University of Manchester, UK and University of Zurich, Switzerland. She also was a partner in the strategically important FP6 EU project EUCLOCK as well as many other collaborative funding schemes (e.g. Scion grant with the University of Zurich). Finally, she serves as the secretary of the European Biological Rhythms Society (EBRS) and as a member-at-large of the Society for Research on Biological rhythms (SRBR). These two societies constitute the central focus for Biological Rhythm Research worldwide and so afford Dr. Sumová a significant international recognition.

## **2. Strengths and Opportunities**

- (1) PI and team are outward looking, are highly recognized and have strong international connections and collaborations.
- (2) Circadian clock research is relevant for most aspects of behaviour, its physiology and pathology. For this reason, the projects pursued by this team could serve as powerful bridges between this group and many other departments within the Institute (e.g. Epithelial Physiology, Neurophysiology of Memory, Cellular and Molecular Neurophysiology, Adipose Tissue Biology, Genetics of Model Diseases and Experimental Hypertension).
- (3) Given the strong links between clocks and elements of metabolism, there is a motivation to develop the metabolomics capabilities within the Institute.
- (4) The team could capitalize on the local environment to strengthen the translational (clinical) elements of circadian rhythm research.
- (5) Future plans look appropriate and should yield strongly publishable results (but also see below).

### **3. Weaknesses and Threats**

While the areas that Alena Sumová's department investigates are certainly highly relevant, the small group size presents a risk of over-diversification and ultimately a reduction in the quality and depth of research. One is left wondering whether the impact of past publications from this group may have fallen short of their full potential as a result.

### **4. Recommendations**

- (1) Focus the research plans on topics where the team is strong and competitive, defined by the expertise of the group and by advantages of the local environment.
- (2) Capitalise on the strong international networking of this group to actively recruit more international postdoctoral fellows and PhD students.

### **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.

#### *Declaration on the involvement of students in research*

The involvement of students in the research is considered excellent by the commission.

#### *Declaration on societal relevance*

The societal relevance of the research is considered very good by the commission.

#### *Declaration on the position in the international and national context*

The commission concludes that the team is internationally competitive, and leading in the national context.



### *Declaration on the vitality and sustainability*

Vitality and sustainability is considered good by the commission.

### *Declaration on the strategy and plans for the future*

The commission concludes that the strategy and plans for the future were convincing, with limitations described above.

## **Team 20: Developmental Epileptology**

### **1. Introduction**

This multidisciplinary team is headed by Dr. Kubova and consists of 4 senior scientists, 1 junior scientist, 3 emeritus scientists and 3 laboratory assistants. During the evaluation period, the group hosted a total of 16 PhD students (of which 7 defended their thesis), 39 MSc students and 4 BSc students. The ultimate goal of the group is to better understand the pathophysiology of epilepsy, to develop new approaches for treatment and to improve diagnostic tools for epilepsy. During the course of the evaluation period, this team generated 82 publications of which 16 have been analysed in depth. Of these, 5 were judged as internationally excellent and 11 as recognised internationally.

This group has developed a basic research approach that involved close cooperation with mathematics, physics and drug development. In addition there is a limited interaction with the pharmaceutical industry in the search for effective age-specific anti-seizure drugs. The primary research topics cover 1) the mechanisms of ictogenesis, epileptogenesis and related disorders in the mature and immature brain, 2) The search for new diagnostic tools for epilepsy, 3) how a pharmacological intervention in neurotransmitter systems can impact on general brain development, 4) The role of oxidative stress in the pathogenesis of epilepsy and 5) the development of anti-seizure drugs. The work involved a broad range of methodology including electrophysiology, histology, behavioural analysis, micro dialysis and in vivo cell imaging.

Research highlights during the evaluation period include studies documenting the extent of brain damage induced by induced seizures on the infant rodent brain (Druga et al., *Brain Res.* 1355: 174-179, 2010). They also revealed that severe seizures result in a prolonged deficiency of the mitochondrial complex I and an associated increase in oxidative stress. Treatment with free radical scavengers partly alleviated these effects (Folbergrová et al., *Neurochem. Int.* **56**: 394-403, 2010; *Exp. Neurol* **233**: 421-429, 2012). Furthermore, the team described the effects of clonazepam, a GABAA/BZD receptor agonist, on the immature brain (Mikulecka et al, *Front. Behav.Neurosci.* **8**:101, and **8**:169, 2014).

## **2. Strengths and Opportunities**

- (1) The group has strong international connections and collaborations within the epilepsy field, and has published numerous collaborative papers.
- (2) The group investigates a topic that is highly relevant with regard to human health.
- (3) The group is strongly engaged in activities of the international epilepsy research community

## **3. Weaknesses and Threats**

- (1) A low proportion of publications involved PhD students as co-authors (31%). This is a strikingly low number given the relatively high throughput of PhD students through the lab.
- (2) There is an intrinsic limit in the utility of the rodent models to translate findings directly to human epilepsy.
- (3) From the oral presentation of the activities, the commission did not gain a clear view of the strategic relevance of the research activities. In particular, there was no mention of clinical collaborations which are clearly crucial for conveying this disease-focused basic research to potential real world applications.
- (4) The commission identified only limited overlap between individual projects in the team.

#### **4. Recommendations**

(1) The clinical aspects should be strengthened, and strategies should be considered how to test the relevance of the preclinical findings in a clinical context.

(2) The internal communication and collaboration should be enhanced with the aim to strengthen synergies between the different parts of the research concept.

#### **5. Detailed evaluations**

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

The commission concludes that the results of the team are overall good, in part very good.

##### *Declaration on the involvement of students in research*

The involvement of students in the research appears inadequately low.

##### *Declaration on societal relevance*

Given the importance of epilepsy and the necessity of better treatment options, the aims of this work have high societal relevance.

##### *Declaration on the position in the international and national context*

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

##### *Declaration on the vitality and sustainability*

Vitality and sustainability appear good.

##### *Declaration on the strategy and plans for the future*

Strategy and plans for the future were sound and convincing, with the limitation that there was no strategy how to pursue the translational aspects (i.e. by links with clinical medicine and/or industry).

## **Evaluation of Team No. 21: Developmental Cardiology**

### **1. Introduction**

The Department of Developmental Cardiology is a very well established group with Frantisek Kolar as the lead. The group consists of the PI, 3 senior and one junior scientist, 3 post-docs, 3 technicians, and currently 4 PhD students. It is overall a medium to large sized group.

The scientific focus of the Department lies on the signalling of cardioprotective effects of chronic and/or acute hypoxia in rodent models of acute myocardial infarct and heart failure. The expertise and standing of the group is internationally recognized in this area.

### **2. Strengths and Opportunities**

- (1) The group presented very good research results with high clinical relevance, based on a well-established, innovative methodology.
- (2) One of the junior scientists from the group gained valuable international experience in US / Canada and could be recruited back to the lab.
- (3) The group has a long track record of a high success rate in grant applications.

### **3. Weaknesses and Threats**

The retirement of the group leader poses the biggest threat and the transition following his retirement as well as future plans have not been fully explained convincingly.

### **4. Recommendations**

The commission recommends developing clinical collaborations as well as to consider employing new models (e.g. transgenic mouse models).

Furthermore, a clear succession plan for the retirement of the group leader is necessary.

## **5. Detailed evaluations**

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

The commission concludes that the results of the team are overall very good.

### *Declaration on the involvement of students in research*

The involvement of students in the research is considered good by the commission.

### *Declaration on societal relevance*

The societal relevance of the research is considered very high by the commission.

### *Declaration on the position in the international and national context*

The commission concludes that the team is internationally very visible, and that it has a pioneering role in the national context.

### *Declaration on the vitality and sustainability*

Vitality and sustainability could be compromised by the retirement of the PI, given his international standing.

### *Declaration on the strategy and plans for the future*

The commission concludes that the strategy and plans for the future were convincing.

## **Evaluation of Team No. 22: Biochemistry of Membrane Receptors**

### **1. Introduction**

This team, headed by Doctor Svoboda, consists of 3 senior scientists and 4 junior scientists (1 currently on maternity leave) which over the course of the evaluation period has hosted 5 PhD students, 6 Masters students and 3 Bachelor

students. In 2014, the former director under the advice of a "Search and Evaluation Committee" group decided to alter the independent status of the group to that of a laboratory within the Department of Biomathematics.

The focus of the team has been to study (1) the mechanisms underlying the desensitisation and hypersensitization of opioid receptors as well as (2) the establishment of fluorescence spectroscopy and confocal fluorescence microscopy as tools to study the effects of cholesterol on the structural organisation of G protein coupled receptors within the membrane. During the evaluation period, this group has published 22 papers in journals with impact factors. Of 7 assessed, 5 were graded internationally recognized (group 3) and 1 internationally excellent (group 2).

## **2. Strengths and Opportunities**

The commission appreciates the establishment of new spectroscopy and microscopy technology.

## **3. Weaknesses and Threats**

- (1) The involvement of students in research publications is low.
- (2) The commission appreciates the expertise and the track record of the scientists in the team. However, the current research concept was not convincing. Specifically, the commission concluded that the research fields (opiate receptor regulation, effect of membrane lipids on receptor function) had been investigated intensely by others during the last decades. The commission doubts that the present experimental approach of the team will lead to original and innovative results.
- (3) There was no apparent concept for capitalizing from the previous proteomic analysis.

#### **4. Recommendations**

The commission supports the decision of the previous Director and the Institutional "Search and Evaluation Committee" regarding the limited future prospects for this as an independent group.

#### **5. Detailed evaluations**

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

The commission concluded that the results are sound but could be improved with regard to originality and innovation.

##### *Declaration on the involvement of students in research*

The commission concluded that the involvement of students in the research is too low and should be improved.

##### *Declaration on societal relevance*

The societal relevance of the research of the group is limited.

##### *Declaration on the position in the international and national context*

The group is visible in the international and national context.

##### *Declaration on the vitality and sustainability*

Vitality and sustainability of the Team are limited.

##### *Declaration on the strategy and plans for the future*

The commission concluded that strategy and plans for the future were not convincing.

**Date:** December 28, 2015

**Commission Chair:** Prof. Dr. Hans-Georg Joost