Recommendations of the International Advisory Board, IOCB

Based on the written and oral presentations of the heads of Teams

Prague, March 20-21, 2010

Dr. Václav Čeřovský (Senior Research Team)

Members of the IAB are aware of the fact that this team started at the most difficult position (dysfunctional, low productivity group with a lot of "historical baggage"), with a clear mandate to completely change the orientation of research and bring in new themes with high potential of scientific impact, as well as practical application. Dr. Čeřovský has chosen the area of antimicrobial peptides and succeeded in mastering the techniques of their isolation, characterization and synthesis. His team has shown that they were able to succeed in characterization of peptides which were unsuccessfully studied by the established groups in the field. However, the IAB noted that the productivity of the team is not yet at the desired level (partially due to the fact that the presented results were achieved by only a fraction of the personnel listed). The lack of external funding (only one grant received to date!) is worrying and may negatively affect this team's future. Furthermore, biological collaboration addressing the mode of action of the peptides should be the priority, if this program is to survive. The presentation of the accomplishments of the team was not properly streamlined, making evaluation more difficult.

The IAB supports the conclusions of the independent evaluators that this group:

- Should focus more attention on the elucidation of the mechanism of action of the novel antimicrobial peptides, especially utilizing the power of synthetic techniques to investigate the structure-activity relationships and investigating modified (labeled) peptides at the cellular level.
- Try to establish collaboration with laboratories interested in the biology of antimicrobial peptides and their mechanism of action.
- Use Lucifensin as the priority target and evaluate its potential as a novel therapeutic agent, with the aim of approaching pharmaceutical companies potentially interested in anitimicrobial peptides.
- Close the research in the area of small molecules.
- Focus the attention to obtaining external grant support for their research.

It is the majority opinion of the IAB that the team should be allowed to continue for the next two years, but that its size be significantly reduced by removal, as soon as practicable, of the unproductive members. Performance of the team should be further reviewed after two years.

Dr. Hana Chodounská (Senior Research Team)

This team has been primarily working on synthesis and characterization of a number of steroids. More than 120 new steroids have been synthesized, mainly to evaluate the basis for their neuroactivity.

This is a long-running project that has been ongoing without major modifications for a number of years, yielding a substantial number of publications. However, the contribution to those papers of this team is not at all clear (was it mainly provision of compounds to outside investigators, or did members of the team provide equal scientific input?). The team consists of a fairly large number of personnel, whose role was not well explained. Whereas very substantial grant support was reported, there were insufficient details to evaluate what fraction of the grant funds would be directed to support the team, and what fraction was primarily for the benefit of the outside collaborators. The incomprehensible presentation of the material during the meeting with IAB did not help in clarifying these matters.

The recently launched collaboration with Dr. Viklicky, a world-class neurobiologist, has poured some new life into the group, attracted external support, and resulted in several good publications and patents. This research is new and is clearly driven by the biologists, relegating the chemists to servicemen, who provide series of compounds for biological testing in an old-fashioned medchem way. This mundane chemistry does not require any special skills and could be carried out by any competent synthetic chemist. The reverse is true about the isotopically labeled compounds, required as analytical standards, where a detailed knowledge of steroid chemistry is essential. However, no really new chemistry has emerged from these efforts to date, which makes the very existence of the steroid group questionable, to say the least. Good collaboration between a biologist and a synthetic chemist should be based on a balanced partnership; not necessarily 50:50 but not as heavily imbalanced as in this case. Dr. Viklicky clearly needs new neurosteroids for his research and these have to be made by someone as they are not commercially available, but the question is, in which setup. The current position is not tenable in a long term and a new solution has to be found: if Dr. Viklicky needs these steroids, he should provide full financial support, including the personnel salaries. However, moving the steroid group to his Institute would not be viable, as synthetic chemists require proper environment. One possible solution would be to make Dr. Chodounska and her coworkers (much reduced in numbers) part of Viklicky's group but located at the IOCB. Alternatively, the existing steroid group (after a reduction) could be absorbed by other synthetic groups. According to this scenario, the existing expertise would be preserved but in the same time the steroid burden would be removed from the shoulders of IOCB.

The majority of the IAB recommends that the team, as currently constituted, should be closed within the next two years, and the existing synthesis expertise of the most productive members redirected to other projects of interest to IOCB, or to projects with Dr. Viklicky, if he is willing to provide sufficient financial support.

Dr. Tomáš Macek (Senior Research Team)

This team is pursuing two lines of research: enhancing the activity of ribulose 1,5-bisphosphate carboxylase (RuBisCO) and bioremediation. This team is split between IOCB and ICT, and the presentation of Dr. Macek did not make it clear at all how the tasks are divided between the two institutes (even when asked repeatedly), perhaps deliberately. It was also very difficult to evaluate the resources available to the team in IOCB, and to determine how many of the publications were actually due to the research that originated there. Data describing grant support were insufficient to evaluate how much effort of the team is financed externally. There seems to be very little in common between the research conducted by this team and the main areas of interest of IOCB, and little collaboration with other groups. On the other hand, it appears that the projects, which might lead to practical results, are much more closely aligned with the profile of ICT.

The large majority of the IAB is in favor of orderly transition of this team to ICT and termination of its support by IOCB (financial and space-wise). This task should be finalized before the next review of the research teams that is scheduled two years from now.

Dr. Peter Beier (Junior Research Team)

The members of the IAB were unanimously positive in their evaluation of the achievements of the team of Dr. Beier during the period 2007-2009. Regarding the next period, in the ensuing discussion it was suggested to Dr. Beier should pay special attention to the following aspects of his research:

- To enlarge the scope of his promising nucleophilic fluorination reactions such as di- and trifluoromethylation, tetrafluoroethylation and tetrafluoroethylenation to nitrogen-containing acceptor molecules (e.g. imines and heterocycles).
- To demonstrate, on selected examples, the usefulness of the investigated methodologies for preparation of fluorine-containing analogs of bioactive compunds. This could enable him to seek for a patent protection for some of his new F-reagents (if not already published).
- To continue the search for new F-delivering reagents and for their applications.
- On carefully selected examples, to show the superiority of biotransformations in perfluorocarbon media by making the most of their specific advantages, e.g. a high oxygen concentration, fewer side reactions vs. water, etc.

An innovative inroad into synthetic organo-phosphorous chemistry, especially in combination with fluorine in the molecule(s), is still a rewarding research goal. However, at least one member of the IAB felt that neither the scientific merits nor the practical results favor the plans outlined in Scheme 7.

The IAB unanimously recommends that the research team of Dr. Beier be allowed to continue for the next two years with at least the current resources, focusing on the potential biological or biomedical applications. The team's progress needs to be rigorously reviewed after the two years.

Dr. Thomas Kraus (Junior Research Team)

The members of the IAB board unanimously recommend the continuation of support for the group of Dr. Kraus for the next period. The external review process has identified some strengths and weaknesses of the current research program, and the IAB is in agreement with these recommendations. Dr. Kraus should, in particular, pay attention to the issues of early toxicity tests of potential artificial membrane carrier molecules and the balance of the breadth of the team's research program compared to available resources.

We are confident that Dr. Kraus research program will develop well over the next years, and are looking forward to the results of the next review in two years time.

Dr. **Lubomír Rulíšek (Junior Research Team)**

It is the unanimous opinion of the IAB that this is the best team among the seven groups that were reviewed at this time, that the selected projects are outstanding, and the publication record truly remarkable. The IAB notes the right balance of subjects that were originated by the team, that were conducted in equal partnership with collaborators, and that provided service to collaborators. This project should be enthusiastically encouraged and fully supported in the future, with the view of converting this team to the Senior Research Team status after the next review in two years.

Dr. **Filip Teplý (Junior Research Team)**

The IAB was generally impressed by the performance of this team. We were most enthusiastic by the work on helquats and would like to encourage Dr. Teplý to synthesize more structures of this kind, perhaps extending to helquats with 4 instead of 2 nitrogens. Potential application may include antiviral activity; as demonstrated for the viologens, and/or antagonization of some 7-TM receptors such as CXCR4. As potential CXCR4 antagonists, these compounds may eventually be useful as stem cell mobilizers. However, in agreement with the external reviewers, IAB would like to encourage Dr. Teplý to further differentiate his areas of interest from those that he pursued as a graduate student.

The IAB unanimously recommends that the research team of Dr. Teplý be allowed to continue for the next two years, with a further review following.