Evaluation of Estonian Research

- Biochemistry -

Report to the Estonian Science Fund Council

by

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NFR Naturvetenskapliga forskningsrådet
Swedish Natural Science Research Council

Foreword

Several Swedish organizations have been asked to take part in a general evaluation of all research performed at academic institutions in Estonia. NFR has agreed to organize the evaluation of Estonian research within the field of natural science. This report has been prepared according to an agreement between the Estonian Science Fund Council and the Swedish Natural Science Research Council (NFR).

During the spring of 1991 Estonian scientists completed reports on their research which were sent to NFR. These reports have subsequently been distributed among 14 Swedish evaluation groups. In total about 40 Swedish scientists are engaged in the evaluations. The groups are making site visits to the Estonian laboratories and institutes during 1991/92 to discuss the research performed, the plans for future activities and to get information about the working conditions, experimental facilities, financial resources etc. Each group has been instructed to produce a report assessing its particular research area.

This report concerns the sub-field of biochemistry and will eventually be a part of an extensive report covering all Estonian research in natural science.

The organization of the site visits is done in close cooperation with the Estonian Science Fund Council. Although difficult times prevail in Estonia all the site visits have been successful. The NFR is grateful to the Estonian Science Fund Council for its efforts to handle all practical matters in connection with these visits.

The NFR is also grateful to the Swedish scientists who with enthusiasm and great skill have taken part in the demanding evaluation work.

Finally, the Council wishes to express its sincere hope that this evaluation report will contribute to a further positive development and strengthening of Estonian science.

Carl Nordling
Secretary General

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INTRODUCTION

The Estonian Science Fund Council has instructed Estonian scientists in the field of Biochemistry to prepare reports concerning their research activities during the last 5 years. These reports were completed during the spring of 1991 and dealt with the following points:

- project leader(s)
- short description of the objectives
- summary of results
- summary of resources
- scientific staff and their qualifications
- list of publications
- dissertations
- scientific meetings organized
- prognosis of the future development of the project

In most cases the reports were accompanied by reprints of scientific publications written in English and Russian.

In July 1991 the reports were sent to NFR and during the autumn the evaluators received the reports. A site visit by the evaluators to the relevant Estonian research institutions was done in the period February 16-18 1992. The Estonian Science Fund Council had appointed Ülo Haldna and Ilmar Koppel as organizers and contact persons for this evaluation.

The research groups visited were: a) At the Estonian Academy of Sciences, Tallinn; Laboratory of Biorganic Chemistry of the Institute of Chemical Physics and Biophysics (Jüri Siigur (head), M Haga, T Kesvatera, M Paberit, P Sikk and V Tougu), Laboratory of Instrumental Analysis, Institute of Chemistry (M Kaljurand), and Laboratory of Physicochemical Investigations - Group of Polysaccharides Research, Inst. of Chemistry (K Truus and A Kollist). b) At Tartu University; Molecular Modelling Laboratory, Institute of General and Molecular Pathology (R Mikelsaar), Laboratory of Analytical Biochemistry, (T Pussa), and Laboratory of Bioorganic Chemistry (J Järv). Each group gave a brief presentation of their work followed by a discussion and question period. A demonstration of laboratory facilities and equipment was normally included.

ACKNOWLEDGEMENTS

We like to thank Drs Ülo Haldna and Ilmar Koppel for their generous hospitality and efforts to make the visit to Tallinn and Tartu very pleasant.

GENERAL COMMENTS ON BIOCHEMISTRY

Before going into the detailed analysis of the various groups we would like to make some general comments and reflections.

It should be stressed that the various projects were evaluated upon their merits within basic research rather than on their applied or commercial potentials. In fact, it was the opinion of the evaluation group that the applied side of the projects was often overemphasized. For example, support for projects not in the international front line aimed at production of certain agents for a protected national market cannot be in the long term interest of Estonia considering the new political situation. The evaluation group has made economic suggestions in connection with the evaluation although the members are fully aware that the difficult economic situation in Estonia may not allow any increased support for research in the near future.

The evaluation group found the divided organization of research in Estonia under the direction of the Academy in Tallinn and the University in Tartu quite suboptimal. We found several duplications where a concentrated effort would certainly be more efficient considering the small size of the Estonian scientific community. This is a general political question and the group does not want to give a detailed recommendation, but certainly the overall organization of research in Estonia is a key question that has to be dealt with. The group recommends that basic research should be based upon a university organization to allow a close integration of research with the teaching of students.

The evaluation group recognized that the facilities with respect to laboratory buildings and equipment urgently need upgrading and renewal. In the long term, the lack of modern laboratories and equipment is one of the most serious problems for Estonian research. In the short term, the lack of immediate availability of certain chemicals and radioisotopes is a big problem.

From a biochemical point of view the groups visited lacked competence and facilities for the modern techniques of molecular biology such as cloning, sequencing, hybridization, site-specific mutagenesis and transformation. These techniques have dramatically influenced research within biochemistry of the western countries and changed the way people do research. It is extremely urgent that such competence is quickly built up through student exchange programs, schemes for visiting scientists and collaborations with prominent groups abroad. Knowledge in molecular biology should be spread into virtually all biochemical research groups and not concentrated into certain centers.

EVALUATION OF RESEARCH GROUPS

Dr. Sci. Mihkel Kaljurand
Laboratory of Instrumental Analysis
Institute of Chemistry
Estonian Academy of Sciences
Tallinn

Computerized Chromatographic Analysis of Nonstationary Substance Flows

Principal activities

The research group has since about ten years ago studied the possibilities of applying computerized multiple input chromatography (correlation chromatography) for different purposes. The aim is to apply computers in chromatography in order both to organize experimental control and for data processing. Special efforts have been made towards decreasing detection limits and improving time resolution. Chemometrical approaches have been used for classification and clustering of different kinds of samples.

Most work has so far been made with gas chromatography, where the methodology has reached such a mature level that it can be used in routine analysis. Special emphasis has been put on studies of polymer degradations, which are performed in an automated fashion involving injections from the reaction mixture on-line to the gas chromatograph followed by automated data evaluation. Methods for environmental analysis have also been developed.

Efforts are also presently being made to use the technique with HPLC, and interesting results have been obtained with the indirect detection principle. The results have to a large extent been published in international journals, and an authoritative book with the title "Computerized multiple input chromatography" has been published (1989).

Evaluation

Dr. Kaljurand is a highly competent scientist and the scientific results and program are very good. Only a few research groups in the world are pursuing this kind of research, and the group has established this research direction in Eastern Europe and made important contributions in developing the methodology of correlation chromatography. The results are published in recognized international journals and the realization of computerized chromatographic methods was assigned as one of the most outstanding achievements in chromatography in the USSR in 1991 by the Chromatographic Council of the USSR Academy of Science.

Recommendations

Based on the very good scientific quality of the group, support is strongly recommended. The structure of the group, comprising research scientist, junior scientists, students and technical staff, seems to be efficient, but it could well be larger; the work is performed in a most cost-effective way. Strong support is needed to modernize the equipment and for running costs in order to continue the very good research programme at the same high level.

Dr. Jüri Siigur
Laboratory of Bioorganic Chemistry
Institute of Chemical Physics and Biophysics
Estonian Academy of Sciences
Tallinn

Biorganic Chemistry of Proteins

Principal activities

This laboratory, now headed by Dr. Siigur, performs broad research in the field of protein chemistry and enzymology. The main activity is the isolation and characterization of biologically active compounds from various natural sources. Studies on proteinases from snake venoms play a central role in this part of the project. Another research activity is focussed on the mechanism of enzymes, involving the role of electrostatic interactions in molecular recognition and binding, using a traditional physicochemical approach. Enzymes such as acetylcholinesterase, trypsin and lipases are being analyzed. For the latter enzyme, its action at an interface between two liquid compartments is studied. One very interesting subproject is the use of proteinases for synthesis of peptides. Of particular importance is the discovery of efficient peptide synthesis at freezing temperatures.

The group has quite a high publication profile including many papers in international journals. The laboratory of Bioorganic Chemistry is currently moving into a newly built laboratory building and is fairly well equipped.

Evaluation

There is no doubt that the group has documented competence within traditional protein chemistry, has shown good scientific production in the past and has good research facilities in new laboratories. The group has therefore a potential for future research within life sciences in Estonia. On the other hand, the current research projects can be subjected to criticism. In the project on isolation of biological compounds from natural sources, the evaluation group found a lack of basic conceptual questions. It was easy to get the impression of a random screening of substances for future use in some applied context i.e. as products for the Kemotex company. This makes the research somewhat unfocussed and superficial. The physicochemical knowledge concerning protein structure, ligand interactions and catalytic mechanisms is quite advanced. However, the research in this field will have no future potential if it is not combined with structural protein biochemistry, site-directed mutagenesis and molecular modelling. The group found the project concerning the lipase enzyme quite vague. The best and most original project is without doubt that concerning peptide synthesis by proteolytic enzymes under freezing conditions.

Recommendations

The only project that merits support at present is that concerning enzymatic synthesis of peptides. The other activities within the laboratory of Bioorganic Chemistry have to be reorganized before any economical support should be given. The research should be focussed on very few enzymatic problems of conceptual interest and not be directed by any particular biological source. Moreover, the long-term survival of the group in an international perspective will require that its very high competence in traditional protein chemistry is combined with the potential of techniques related to molecular biology. It is therefore of crucial importance that the group gets involved in exchange and collaborations with prominent western laboratories to quickly get in-house knowledge of molecular biology. After such changes in direction, the group, considering its present competence and experience, should be able to play an important role for future Estonian protein research. After a re-evaluation of the group within 2-3 years more general support from the Estonian Science Fund Council should be considered.

Dr. Kalle Truus
Laboratory of Physicochemical Investigations
Institute of Chemistry
Estonian Academy of Sciences
Tallinn

Preparation, Characterization and Utilization of Red Algae Galactans and Sorbents on Their Basis

Principal activities

Different kinds of marine red algae were collected from different parts of former USSR, and their content of polysaccharides (sulfated galactans) were isolated and characterized. Standard procedures were used to determine different parameters: ash content, sulphur content, mechanical strength, gelling temperature, solidification temperature and electroosmotic properties. The materials were further characterized by ^{13}C-NMR-measurements (methoxyl-content), neutron activation analysis and X-ray analysis. Based on obtained data the most suitable polysaccharide was selected to produce high quality agar and agarose. A large variety of sorbents for use in separations has been synthesized. Studies on the gelling mechanisms of the polysaccharides have recently been initiated.

Evaluation

The polysaccharides have mainly been studied by conventional techniques and standard procedures, and the synthesized sorbents mimic materials earlier produced in Western countries. The selected raw material for production of high quality agar and agarose is from a source in Russia, and may not be so easily available to the group in the future. The studies on gel forming mechanisms were in a preliminary stage, but are of a more basic scientific nature and should be encouraged. This necessitates co-operation with groups experienced in related physicochemical studies. The published papers were mainly written in Russian in domestic journals and not available to the evaluators. The group is competent regarding the present activities oriented towards applications, but studies on basic research are lacking.

Recommendations

The group has mainly been occupied with work on the production and standardization of agar and agarose for commercial purposes. No results from basic research activities have been published, although studies on gelling mechanisms of agarose have been initiated. Based on the data presented, support for basic research cannot be recommended for the group.

Prof. Jaak Järv
Laboratory of Bioorganic Chemistry
Tartu University

Specificity and Mechanism of Action of Enzymes and Receptors

Principal activities

Prof Järv has very successfully used detailed kinetic measurements - "biokinetics" - to study the mechanism of cholinesterase-catalyzed reactions. A stereochemical model for acetylcholinosterase and butyrylcholinesterase was proposed already in the early 1980s, based on experiments with different inhibitors and substrate analogues. This model has been very important for further work in this field. Very interesting kinetic studies have also been made on muscarinic receptor-antagonist interactions. At least two steps were identified, an initial very fast binding step and a slow isomerization step. The results show the importance of making receptor kinetic studies instead of only binding studies. To further characterize molecular recognition, the group changed fields some years ago and started to study protein kinases. Here structure-activity studies combined with kinetic analyses are used to follow protein - peptide interactions. A new assay system was worked out allowing easy detection of phosphopeptides. So far these studies have been made on protein kinase A and C and synthetic peptides have been used to define a "minimal substrate".

Evaluation

This dynamic group has during the last 15 years produced many very interesting results of very good international standard. The data has been published in well known international scientific journals of high impact value. The group has attracted many very good students and a great number of international collaborations have been established. Järv has also made very important investments for the future by sending out his students as post-doctors to leading laboratories all over the world to learn molecular genetics, 2-D NMR and how to express and prepare G-proteins.

Recommendations

Support for this group is most strongly recommended based on the very high productivity and high quality of the presented research. The work focusses on very significant problems and the experimental approach is realistic and up to date. It is of utmost importance that the group obtains proper laboratory space and equipment to be able to attract the earlier mentioned post-doctors so that they return to Estonia.

Dr. Sci. Raik-Hiio Mikelsaar
Molecular Modelling Laboratory
Institute of General and Molecular Pathology
Tartu University

Investigation of Macromolecular Structure by Atomic Models

Principal activities

Mikelsaar graduated from the Medical faculty and served as a pathologist and an immunologist at Tartu University up to 1979. Then he started to work on molecular modelling and developed plastic atomic-molecular models for which he received his doctorate in chemistry from Moscow 1989. These models are now patented in a number of countries. Using data from the literature, Mikelsaar uses his plastic models to construct various biomolecules such as the codon-anticodon complexes in tRNAs, biomembrane lipid bilayers and polysaccharides and from these models he predicts new interactions. In parallel, Mikelsaar has published some theoretical papers on evolution claiming that mitochondria have not evolved from eubacteria but from more ancient predecessors.

Evaluation

Mikelsaar works quite isolated from theoretical chemists and computer molecular modelling experts in a very small laboratory together with two technicians who assemble the models. He has one graduate student from Experimental Physics who is doing computer energy minimizing studies. With the heavy competition from the extremely rapidly growing computer modelling and molecular dynamics studies in the Western countries, it is difficult to see any future in basic science for these types of studies.

Recommendations

The plastic atomic-molecular models should still be of interest for basic teaching in chemistry and therefore this project should be self-funding as long as it can. Apart from that, no further funding, except for Mikelsaar's salary, is recommended for this project.

Dr. Tonu Püssa
Laboratory of Analytical Biochemistry
Tartu University

Investigation of Methods for Separation, Purification and Analysis of Lectins and Blood Plasma Proteins

Principal activities

Püssa was earlier involved in the large agarose project where high-quality agarose was prepared from seaweeds collected in the former USSR. This was a joint project with Truus and Kollist at the Institute of Chemistry of the Estonian Academy of Sciences in Tallinn. The agarose was used to manufacture beaded gels for chromatographic purposes and for electrophoretic separations. Now Püssa wants to use his earlier knowledge of agarose beads chromatography to set up a production unit for the purification of a number of human plasma proteins of medical interest. He recently returned from a 5 months visit to the Finnish Red Cross Transfusion Service in Helsinki where he studied the fractionation of plasma proteins. There silica material was used to adsorb out certain proteins and he now wants to replace the silica material with less expensive ones. The other project proposed by Püssa is to develop lectins for use in the fractionation of bone marrow cells. This technique is then to be used to prevent graft versus host reactions after bone marrow transplantations.

Evaluation

The agarose project was successful in the earlier days. However, today this is only of technical and commercial interest since no substances new and original to the international scientific community were ever produced. Likewise, the manufacturing of plasma proteins is important but contains very little of interest to basic science. In spite of Püssa's visit to Helsinki, he appears to have rather limited earlier experience in protein purification. The lectin project contains very little substance and the main reasons while it was initiated appears to be historical ones - the first lectin, ricin, was discovered in Tartu 100 years ago. Püssa's lack of laboratory facilities and experience in this field appear to be very difficult obstacles for successful work. Cooperation with the Laboratory of Hematology in Tartu is mentioned but the chances that this project will produce new and interesting results are low.

Recommendations

Most of the projects presented by Püssa are mainly of technical, applied interest and contain very little basic science. Therefore, support for these projects cannot be recommended. Instead, the members of the group should be encouraged to change fields if they want to stay in basic science.

APPENDIX

Background of evaluators

Bertil Andersson

Professor and Head of Biochemistry Department, Stockholm University. His research concerns biochemistry and molecular biology of photosynthesis. The research includes functional and structural studies of photosystem II and the dynamic organization of the photosynthetic membranes. He has also been involved in the development of methods for separating membrane particles in particular the aqueous polymer two-phase partition procedure.

Lars Thelander

Professor of Physiological Chemistry, presently at the Department of Medical Biochemistry and Biophysics, University of Umeå. His current research interests are molecular genetic studies on the regulation of mammalian gene expression, enzymology and protein chemistry.

Douglas Westerlund

Since 1984 Professor of Analytical Pharmaceutical Chemistry at the Faculty of Pharmacy, University of Uppsala. His current research interests are in separation techniques, mainly HPLC and capillary electrophoresis, applied to studies on drugs and biomolecules. The main theme of the research involves basic studies on secondary equilibria in the separation techniques and their applications to drug purity studies, chiral separations and bioanalytical procedures.