

THE LATVIAN INSTITUTE OF ORGANIC SYNTHESIS – QUO VADIS?

After the collapse of the Soviet Union the Latvian Institute of Organic Synthesis (IOS) landed up in a very complicated situation, since in the face of the ruling parties of that time the young state of Latvia suffered partly from a misunderstanding of the role of science in the development of the nation's economy. The spirit of the thirst for reform reigned throughout, but there was no true vision of what should be reformed. Everything seemed very simple—abolish all the old order, and everything would stay in place!

This is where we started. The Latvian Academy of Sciences was transformed from a union of scientific–research institutes into an academy of only personally elected members. Thus, all the institutes as if obtained independence, while any coordination of the research activity of the teams of scientists ceased.

At the same time it was decided to alter radically the funding of science – the basic funding of the institutes as scientific establishments terminated, and all the resources allocated to science were distributed among the branches of science and exclusively among scientific projects gathering the highest levels of expert appraisal. Here, for three years running the funding was allocated exclusively to theoretical investigations, and the institutes have been obliged to close all the applied subjects.

It was also decided to break down the infrastructure of the institutes, having separated from them the design office and the experimental production facilities, which were either privatized or closed altogether. All this took place against the background of the abolition of the patent law protecting copyrights to inventions of the former USSR, which had previously guaranteed large-scale research centers, such as the IOS, deductions for the industrial use of scientists' inventions.

Scientific collaboration also practically ceased between the IOS and the leading scientific centers of the former USSR, which also suffered from a shortage of funds for science. At the time of the collapse of the Soviet Union IOS had more than 220 contracts on scientific–technical collaboration with other institutes of the country. Now it has to account only for itself.

Here reforms were not concluded, and all the research institutes that were not integrated with universities were deprived of the right to train graduate (doctoral) students, and their scientific councils on the defense of doctoral theses were liquidated. The right to confer scientific degrees remained only with the universities. It was soon decided to change to a single-stage system of degrees for scientific qualification.

The funding of academic science was also greatly curtailed, and this could not fail to bring about a reduction in the research activity of the scientific organizations and a marked decrease in the influx of young people into science. Moreover, the freedom of movement and the more attractive employment conditions in foreign scientific centers could not fail to bring about the departure of scientists to western countries.

The IOS also suffered since many workers left to work in Israel, the USA, Canada, Germany, Sweden, Japan, and other countries. However, the IOS suffered most as a result of the fact that the department of molecular biology and the vivarium were separated from the Institute, and the laboratory buildings of the subdivisions engaged in the study of the medical and biological characteristics of potential drugs were taken out and privatized. The unfinished biological test center, in which it was planned to perform experiments on laboratory animals in accordance with the rules of good laboratory practise (GLP) and to conduct tests on the

toxicological and pharmacological properties of up to four drugs annually, also passed into private hands. The IOS has also lost almost the entire department of drug standardization of, which has become the framework for the state system for the registration of new drugs – the Latvian Drug Agency.

In such circumstances the management of the IOS took a difficult and painful decision – to concentrate mainly on contract researches according to the requests of western pharmaceutical companies!

This was quite a difficult decision, since before this the IOS's main customer for scientific–technical investigations was USSR State Committee for Science and Technology, from which it was no longer possible to expect orders. The financial resources of the IOS also remained at the Vneshekonombank (Bank for Foreign Trade) in Moscow, and contacts with western firms had to be re-established since it was no longer possible to make them through Medexport.

However, this decision proved correct. The Institute quickly adapted to the rules of international cooperation and scientific research in accordance with international standards. In cooperation with the German firm "Merz" the Institute went on to establish its own infrastructure – it created an analytical laboratory for the investigation of API (Active Pharmaceutical Ingredient) and final dosage forms, and then a group of clinical trials.

Scientists at the Institute quickly gained experience in the development of drugs in accordance with the world standards of good laboratory practice and good clinical practice (GCP). Immediately after this it created the first laboratories engaged mainly in the search for and study of novel drugs to meet the requirements of western pharmaceutical companies. And success was not long in coming, since the partners were convinced of the high qualifications and creativity of the scientists at the IOS.

A laboratory was created for the synthesis and investigation of products for the treatment of Alzheimer's disease, and the first clinical trials according to the rules of c-GCP (double blind randomized controlled many-center trials) were set up and were upheld by audit of the experts of the FDA (Food and Drug Administration, USA). Contracts were then received from Japanese, Swedish, English, American, and other firms – both from the large international corporations and from the small pharmaceutical companies.

Collaboration developed on four levels of complexity. The IOS started from the first and least attractive activity – the simple synthesis of the drugs or intermediates required by the customer. With partners that had been convinced that IOS could fulfil orders promptly and efficiently the inquiries soon became more complex.

The second level of collaboration involved the development of preparative methods for the synthesis of drugs. The shortest possible execution times and the high quality of the investigations persuaded our customers to trust the Institute with a more complex task, which is the key task in medicinal chemistry, i.e. optimization of the structure of the potential candidates into drugs. Our collaboration with our western partners thus passed onto the third level.

Finally, the Institute began to receive orders for the complete cycle of discovery and preclinical development of new drugs. The pharmaceutical companies began to turn to IOS for help in the search for new original drugs from zero, i.e. the customers trusted the scientists at the Institute to handle the idea of the creation of a new drug and optimization of the obtained structures, and the modelling and investigation of the structure–activity relationship, including screening of the compounds and evaluating their bioavailability and predicting their possible pharmacodynamic characteristics.

Thanks to the effectiveness and innovation the team at the IOS obtained many new patents, and the first of the new drugs have entered the phase of clinical trials and have moved successfully on to registration.

A large number of orders has affected the Institute's financial position. The infrastructure of the Institute was modernized, and a large amount of analytical and research equipment was purchased, including NMR spectrometers at 400 and 600 MHz with a cryoprobe and with a HPLC unit attachment, liquid-liquid chromatography tandem mass spectrometers (LC-MS-MS), gas-liquid chromatography mass spectrometers (GC-MS), X-ray diffraction apparatus, an ESR spectrometer, elemental analyzers, microwave synthesizers, parallel pulse chromatography preparative instruments, and a lot of other equipment.

THE IOS IN THE THIRD MILLENNIUM

The President of the Latvian Republic V. Vīķe-Freiberga and I. Kalvinsh after the presentation of the Order of Three Stars, 2006



The management of the IOS. From left to right: Deputy Director O. Pugovičs, Deputy Director D. Kārkle, and Director I. Kalvinsh

G. Duburs, I. Kalvinsh, and Scientific Secretary I. Tutane discuss the contents of the display



Working with the new Instruments



I. Kalvinsh proudly demonstrates the new NMR spectrometer to the guests



N. Jaunkalna



S. Grīnberga

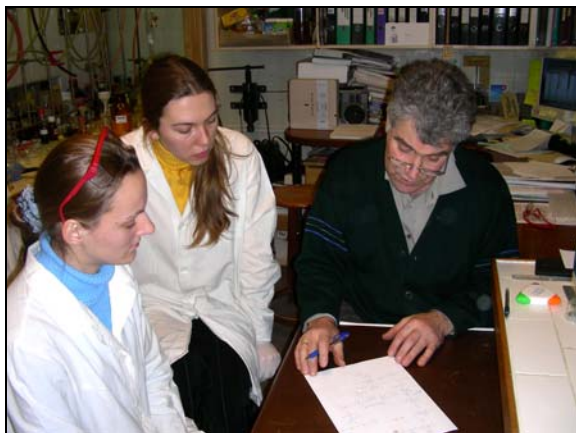


L. Baumane



E. Liepinsh, Head of the Laboratory of Physical Organic Chemistry, and M. Petrova are delighted; the experiment confirmed the calculations

Day by day in the Laboratories



Laboratory students listen attentively to Head of the Laboratory of Organic Chemistry P. Trapencieris



L. Kauliņa



S. Beļakov explains the results of X-ray crystallographic analysis to trainee chemists M. Arkhangel'skii and A. Bernana



E. Erdmane



K. Mekšs



Head of the Laboratory of CNS-Active Compounds V. Kauss with colleagues M. Teus and A. Gutcait



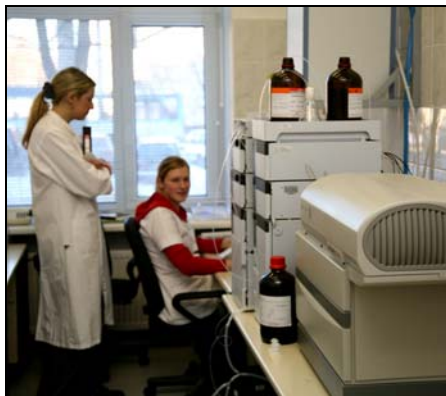
Heads of laboratories E. Loža, P. Trapencieris, and E. Sūna



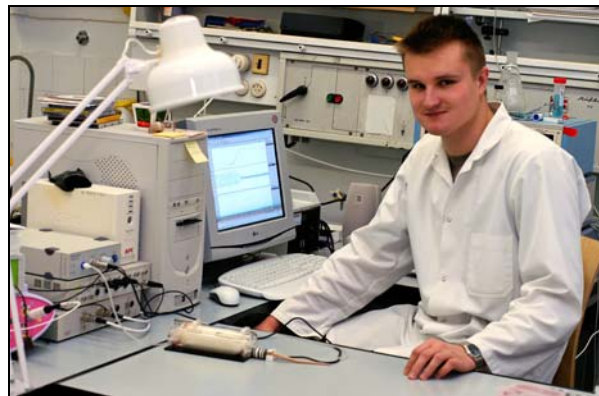
K. Dikovskaya and E. Loža



B. Vīgante and L. Intenberga



Doctoral students A. Kotova and A. Vanaga



Doctoral student of the Laboratory of Pharmaceutical Pharmacology J. Kuka

The influx of young people into the Institute has resumed. Now more than 90 students are engaged in science in the laboratories of the IOS, and doctoral theses are being worked on. The Institute has also been successful in the production of state-financed scientific projects, completing nearly 63% of all the state's theoretical and fundamental researches on chemistry.

The IOS is the leading institution in two state programs. Doctors and professors have returned to the IOS from Sweden, Japan, Germany, and other countries. International cooperation is evolving, and many of our young scientists are studying and working in various universities over the world.

Government policy with respect to science as a whole and to the IOS in particular has changed. Thus, in the critical days for the IOS the proportion of government money in the Institute's budget did not exceed 16%. Now, we calculate that the proportion of state funding in the jubilee year of the IOS foundation will amount to 50%. The basic funding of the Institute was renewed. The IOS has gained access to the financial resources of the European Union, having won the competition for projects on the development of a research infrastructure for innovative work of small and medium establishments, plans for the modernization of the scientific infrastructure, and others.

The average reward of scientists at the Institute has increased several times over the last few years and for the best of them approaches the wage in the European universities.

What are the problems the Institute must face in the very near future?

First, questions concerning the protection of intellectual property, since the Latvian state does not at present support for patenting of inventions.

Second, the IOS must pass on to the next level of its facilities, i.e. to the complete cycle of preclinical investigation of new drugs. But this means that the Institute needs to consolidate radically its scientific and technical base – to create a center of medical-biological investigations, operating according to the rules of GLP in order to have the possibility of conducting preclinical trials in accordance with the requirements of the EU and the USA in this field.

Third, the IOS has started on the planning of a new experimental base for the development of synthesis techniques and small-scale production in accordance with the rules of c-GMP (Current Good Manufacturing Practice). This will enable us to conduct all the necessary investigations to obtain permits for clinical trials of new drugs in any country of the world.

Fourth, for more successful application of contemporary approaches to the search and investigation of new drugs (molecular pharmacology, gene and protein engineering) the IOS is conducting negotiations with the Latvian Biomedical Research and Study Center (BMC) on the creation of a Center of Competence in the development of original drugs. The bones of the BMC comprise the staff of the former IOS Department of Molecular Biology, which in due course was separated as an independent Institute. The two sides were united in the understanding that the potential of the IOS in the design and synthesis of biologically active substances requires screening tools – cloned proteins (receptors) – and also in the detection of new targets for the influence on various diseases.

In turn, the BMC requires new ligands for the receptors and evaluation of the pharmacological significance of new proteins. The joining of forces of the staffs of both institutes is already taking place today within the scope of the state program on the development of new drugs, and in the future this collaboration should be on a more formal basis in the form of a Center of Competence.

Fifth, preparatory work is going on for the re-creation in Latvia of a cluster of chemical–pharmaceutical plants and research institutes as well as universities for the purpose of consolidating the whole scientific and technical potential of the nation in the successful development of new drugs and vaccines and also diagnostic agents. The brain center of such a cluster will be the above-mentioned Center of Competence, to which the teams of scientists working in other scientific-research establishments are added.

Within the scope of such a cluster it is also planned to create a business incubator for innovative establishments of the chemical pharmaceutical and biotechnical region, which will serve as a reference point for the formation and development of new companies in this region. Biotechnology and organic synthesis require

specific laboratory facilities and equipment as well as analytical instruments. Therefore, in the initial period small and medium enterprises will undoubtedly need the scientific and technical potential of the Center of Competence and government support and also financial assistance from the European Union. Consequently, for the more effective use of the costly scientific equipment and the limited resources of highly qualified specialists it is expedient to create such a business incubator at the Center of Competence.

It is obvious that such newly created subdivisions of the IOS as the Center for Biomedical Trials and also the Pilot Plant for biologically active substances within the framework of the cluster should be supplemented by the production of the products from protein engineering and biotechnology (fermentation). Animal breeding house is also needed for the growth of experimental animals for toxicological and pharmacological investigations in accordance with the rules of GLP. At the present time negotiations are going on with the Riga City Council about the creation of a new science park, the first subjects of the infrastructure of which will most likely become the new buildings of a BMC, pilot plant, and business incubator of the IOS.

When the creation of the above-mentioned components is complete the cluster of the chemical pharmaceutical industry of Latvia will undoubtedly be capable of competing with many pharmaceutical companies of the world and bringing great gains to the nation.

Finally, a system for staff training is required and will be put into effect in the changes, since the removal of the IOS and other leading research institutes from the training of highly qualified specialists will lead to a great loss both in the quality of training for young scientists and in the choice of subject matter for the problems being tackled. In this connection the Institute has set itself the task of creating a system for the training of doctors at the IOS in order to train not less than 15 doctors a year, which is vitally important for the successful reproduction and development of the scientific potential of the Institute.

As its fiftieth anniversary is approaching, the Latvian Institute of Organic Synthesis is full of optimism – the period of adaptation to the new operating conditions has ended, and the period of rapid development has begun. The IOS's main strategy in this period is verifiable coordination of the subject matter of the fundamental scientific investigations with the practical applications that the pharmaceutical industry needs to solve. This will make it possible to apply the developed resources to the development of the infrastructure that is primarily essential to fundamental science.

The development of the fundamental problems of the chemistry of heterocycles still plays its role among the divisions of the Institute, since many if not the majority of the drugs have been created on the basis of heterocyclic compounds. A graphic illustration of the significance of this department is the publication of the international journal "Chemistry of Heterocyclic Compounds" in Russian and English, which has been already lasting for more than 40 years.

Under the conditions of globalization only in the balanced development of both theoretical and applied investigations can a research institute in a small nation find its niche and position in the general scientific and technical space. The Institute has proved the justification for such a policy in practice and intends to develop it in the future.

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