Development and Application of Modern Biotechnology

Introduction

Historically, biotechnology can be divided into three groups

- Fermentation processes are mostly concerned with improvement of new phyla of microorganisms and their innovation in the course of their cultivation.
- Use of biotechnological processes for elimination of toxic and other wastes and for transformation of these wastes to non-toxic compounds that can be further utilized.
- Techniques of genetic and cellular manipulation followed by cultivation of animal cells, plant cells and microorganisms.

Cellular and genetic engineering are often included in modern biotechnology. Their era started in the 50s when the structure of DNA was discovered. It is surprising how quickly thousands of products based on this technology came on the market. The use of hybridom technology in the synthesis of monoclonal antibodies came furthest. Currently, 25 000 hybridoms producing monoclonal antibodies against a variety of antigens and with very diverse properties are used commercially. Monoclonal antibodies or their derivates are used in the research, preparation and production of diagnostic procedures and, so far, only rarely for therapeutic purposes. Genetic engineering achieved to prepare a series of products used not only for the purpose of diagnosis and synthesis (recombinant proteins), but also in the therapy of diseases, such as diabetes mellitus, anaemia and some types of tumours.

Mapping out the human genome resulted in a joint achievement of scientists from many countries in the year 2000. We are, however, still at the beginning in the use of this great potential arising from this discovery. Only new achievements in the field of functional genomics and pharmacogenetics will bring a variety of new products onto the market and thus enable us to improve the quality of life. There are many expectations concerning introduction of gene therapy in the therapy of some serious diseases into clinical practice. This is, however, just the beginning as well. Fundamental changes in diagnostic algorithms, together with many worries, arise from bringing the knowledge of individual genoms to practical use. Although modern biotechnology will provide help in a short period of time (in some cases it already does, e.g. still growing human population and its nutrition, or the problem of environmental pollution) the reality will apparently be more complicated. Next to revelation of particular genes and their mutations, it is necessary to learn and understand primary and secondary genetic modifying factors that participate on the final clinical manifestation of the observed gene.

A feature that is typical for the field of modern biotechnology in the Czech republic is the unclear differentiation and fading of basic research, applied research and production in particular institutions. The best basic, as well as applied, research is performed at institutes of the Czech Academy of Sciences (CAS) and at some university establishments. It is not a problem but rather an advantage. Nevertheless, the problem is that production is often placed here as well. These institutions are, however, financed from the state budget and newly developed technology and products are not forwarded to the same places as they are in other countries, i.e. to small and middle-size companies. Vice-versa, businessmen are in a great disadvantage when they try to introduce new biotechnological production. Another factor that contributes to the problem concerning development of small or middle-size biotechnological companies is the tendency to publish all new information in scientific articles even though they contain new pieces of knowledge applicable in practice. Another problem is the industrial research and development of new technologies that is, to a high extent, financed from the state budget with small financial contributions coming from foreign companies.

Suitable projects for the starting Czech entrepreneurs are then absent. Support provided for the development of enterprise in biotechnology, so self-evident in most countries in a form of special programs with respect to specific characteristics of this field (higher costs and longer period of development) is lacking in our country. A program similar to those issued abroad cannot be found in the materials of any programs announced.

A result of the current situation is that, although there is a large number of small and middle-size firms employing a majority of the manpower of our country, the number of biotechnological firms and the number of their employees is negligible in the Czech republic. Tens of biotechnological firms get lost in tens of thousands of small and middle-size firms of all fields and hundreds to thousands employees are negligible compared to millions of other professionals. In this situation, it is difficult to discuss the geographical distribution of biotechnological companies or their share of the total financial turnover in this country.

The basics of biotechnology

Currently, advancements in modern biotechnology are based mostly on information coming from basic and advanced research in molecular biology and genetics. Apart from the already mentioned information resulting from mapping out the genome of various organisms, bioinformatics, functional and structural genomics and proteinomics, study of molecular interaction and systems and molecular medicine will probably be the fields able to bring new fundamental information applicable in the development of new biotechnology. For example, structural genomics together with computer modelling is able to prepare a 3-D model of any protein. From here it is only a step to specific practical use in the development of completely new types of medicaments. Understanding elementary processes that occur in live organisms, as a result of research in cellular biology, virology, immunology and developmental biology, will very quickly find its application in new technology.
As in basic research, there are also fruitful interactions in biotechnology among other fields, such as physics or chemistry, which may seem too out-of-place at first sight. Nevertheless, newly developing areas of research, such as nanotechnology, chip technology and practical applications combine information from these fields. In basically all the areas mentioned above the Czech republic has a number of professionals and scientific groups of very good quality on the level of basic, non-oriented research, as well as advanced, oriented research. Projects in the field of molecular genetics are carried out by many groups at institutes of the Czech Academy of Sciences, for example at the Institute of Molecular Genetics, Institute of Microbiology, Institute of Molecular Genetics of Plants, Institute of Biophysics, Institute of Parasitology, Institute of Experimental Botany, Institute of Entomology, Institute of Experimental Medicine, Institute of Organic Chemistry and Biochemistry. Very good results are also provided by members of research teams at the 1st Medical Faculty of the Charles University in Prague, Medical Faculty of the Palackého University in Olomouc, at the Faculty of Biology of the Charles University in Prague and Masarykova University in Brno. It is also interesting that very good basic research is carried out also by some private companies, for example the Generi Biotech, LTD in Hradec Králové. Subjects outside the Czech republic to the detriment of the cause, later apply plenty of problems focused on by advanced research to practical use. Research in the field of nanotechnology and biosensors is carried out at colleges of biology and technology (Faculty of biology of the Masarykova University in Brno, ČVUT-Czech College of Technology, Prague).
While research in virology is insufficient in the Czech republic (and what is left of it is scattered into small groups of various institutions-Institute of Molecular Genetics of the CAS, Institute of Haematology and blood transfusion, Prague), research in immunology,

developmental biology, cellular biology and pathology (to mention at least some outstanding fields) are traditionally on a high level and are well-performed at many institutes of the Czech Academy of Sciences, together with medical and biological faculties of most of our universities.

Main trends and outcomes of modern biotechnology in the Czech republic

Fermentation technology

Fermentation technology is one of the oldest fields of biotechnology with a long history in the Czech republic. Synthesis of fermentative ethanol from melasa, crude alcohol from potatoes, baking yeast or fermentative vinegar is still in the program of many companies. Here we must not forget to mention the production of drinks, sparkling wines, or beer. New products of this field include medicaments, especially antibiotics, but also precursors of psychoactive substances. Production of those is also traditional in the Czech republic. Series of new medicaments are synthesized chemically. However, it is often a very expensive procedure; the use of microorganisms in these procedures makes them cheaper and simpler. Bacteria and mushrooms are effective means of production of secondary metabolites widely used in many fields. Among these there are antibiotics, substances used in the therapy of tumours, herbicides, pesticides, various immunomodulators and others. There are ways to increase production of these substances or to partially modify characteristics of the substances produced. A classic, but still abundantly used, method of using induction of mutation followed by selection has lately been complemented by a method of genetic engineering, in which selected substances are inserted into the genome of productive micro-organisms. The first method enables us to increase production of secondary metabolites significantly. The problem is, however, that by using this procedure we also increase production of other substances; the method does not enable us to make a selective increase in the production of the substances we desire. On the other hand, the other method enables selective production of a substance of our choice.

All these problems are being researched at a number of laboratories in the Czech republic. The topics of basic and applied research concerning this area of interest are carried out by a number of scientific groups at the Institute of Microbiology of the CAS, Institute of Organic Chemistry and Biochemistry of the CAS and at several departments of the College of Chemical Technology in Prague. Production of cyclosporin can be mentioned as an example of a successful solution. Production of cyclosporin, a very effective immunosuppressive substance routinely used in transplantation programs, is guaranteed in the Czech republic by Galena Opava. Another example is production of veterinary drugs avermectin and monensin and an immunomodulator ascomycin. Nisin and a series of other substances, which are either prepared for production or they are in the stage of being tested, are awaiting their chance to be put into use.

Due to appropriate grant policy and promotion, there are many environmental-concerned projects, which are carried out using fermentation technology, in the Czech republic. Many laboratories of the institutes already mentioned above solve problems of bioremediation, for example elimination of organic substances (PCB, PAH), binding heavy metals, cleaning sludge and liquidation of wastes. In all these projects, classic fermentation procedures are used combined with methods of molecular genetics.

A specific chapter is represented by cultivation of plant cells. In our country there are also several groups, especially at the institutes of the CAS, which participate on these problems. The projects are clearly focused on practical applications, such as cultivation of algae in fermentors or in thin layers which serve as a source or raw materials for the pharmaceutical

industry or as nutrition additives (MBÚ Třeboň of the CAS), production of some efficient medicaments, which are still extracted from plants (taxol, Institute of Organic chemistry and Biochemistry of the CAS). Another stage in the use of these substances is their chemical modification in order to improve their characteristics that can be used in practice. This approach is used at some institutes of chemistry of the CAS, as well as some university laboratories (Faculty of Biology and Faculty of Medicine of the Palackého University). Plant cells are more and more used in elimination of wastes (phytoremediation). In connection with cultivation of plant cells, it is necessary to mention new approaches to plant cultivation which use an explanted culture of plants which contribute not only to improvement of planting, but also to production of stable materials for cultivation of several cultivated plants.

Hybridom technology in preparation of monoclonal antibodies

Kohler and Milstein announced construction of first hybridoms in 1975. In several years that followed, this technology not only became widespread, but particular steps of this technology have undergone improvement as well. Further development led to simplification of the whole procedure to such an extent that it is possible now to prepare antibodies to any immunogen. Due to existence of appropriate myelom line of mice and rats, basically all monoclonal antibodies are of this origin. While any patent does not protect mice of the myelom line, the rat line is patented. This is the main reason why most of the hybridoms are of mouse origin. While construction of new hybridoms is time-consuming and technically complicated, production of monoclonal antibodies is simple and cheap. This is accomplished in two ways, either under in-vitro conditions in different types of fermentors and cultivation bottles, or in vivo in ascitic fluids in mice and rats. Monoclonal antibodies shortly proved to be an indispensable component of many diagnostic sets in human and veterinary medicine. Monoclonal antibodies are routinely used in research and production, however, their use in the therapy of serious diseases, such as tumours, neurodegenerative diseases, and others have not come up to expectations yet. Especially their use concerning applications to the human body promises great progress. This, however, depends on the further technological development and synthesis of monoclonal antibodies that would contain majority of the human component. The use of heterogeneous antibodies (mostly of the mouse origin) leads to many side effects, which are eliminated when monoclonal antibodies are used in vivo. Therefore, there is currently a lot of effort all around the world is put to preparation of so-called humanized antibodies. The technology of their preparation is a combination of hybridom technology and the process of synthesizing recombinant proteins. ScFv fragments of antibodies have half of the size of the Fab fragments, they are less immunogenic, show better penetration into tumours and they can be fused with other proteins or peptides. Potential applications include tissue imaging and targeted application of medications, toxins and radionuclides to tumours.
Another problem in the use of monoclonal antibodies for therapeutic purposes is their relatively low efficiency, for example in the elimination of tumour cells. Improvement of their efficiency can be achieved by preparing so-called immunotoxins. Immunotoxins are complexes of monoclonal antibodies and an effector-active substance, such as various toxins and radionuclides. The resulting complex keeps its specificity of a monoclonal antibody and, at the same time, takes advantage of the strong effect of toxins (radionuclides) in elimination of the target cell. Combination of two different binding specificities, typical for so-called bi-specific antibodies, can increase the selectivity and efficiency of therapeutic antibodies.
Since 1980, the hybridom technology has been used at several research establishments in the Czech republic. Next to several research groups at the Institute of Molecular Genetics of the CAS, monoclonal antibodies have been also prepared at the Institute of Experimental Botany

of the CAS, Institute of Haematology and Blood Transfusion in Prague, a hospital in Hradec Králové, Masaryk's Institute of Oncology in Brno, at the Medical Faculty in Olomouc and scarcely at some other places. Although, we successfully managed to catch the onset of this technology several years ago, there is currently no such project that would be concerned with further development of this technology. At the same time, it is being proved just now that hybridom technology combined with the processes of preparation of recombinant proteins enable us to solve some long-time problems in the use of monoclonal antibodies in the diagnosis and therapy of the human body.
Express systems in the production of antibodies and fragments of antibodies include bacteria, yeast plants, plants, insect and mammal cells. Each of these systems has its advantages, potential applications and restrictions. Bacteria cannot produce complete, glycosylated proteins; they can be, however, used in the synthesis of fragments of antibodies. Antibodies expressed in yeast plants include multi-branched oligosaccharides with a high content of mannose. As well, antibodies produced by plants or insect cells include carbohydrate structures different from those found in mammal cells.
On the other hand, new hybridoms producing antibodies mostly for the use in scientific projects are still prepared in a series of research establishments. These antibodies are, however, also used for practical purposes.
Phage display technology from recent years proves to be a revolutionary method. It enables us to acquire completely new antibodies with high affinity to any antigen outside the immunity system without using animals.

The use of stem cells, cloning

The therapy of infertility by in vitro fertilization (so called test-tube babies) is already a routine approach used in many countries, including the Czech republic. Routinely, hundreds of embryos are prepared this way but only a part of them is used. The rest of them are destroyed after some time. Cells forming an embryo are characterized by not being differentiated, i.e. they still have not lost the ability to create a completely new individual and, under certain circumstances, they are able to develop, for example, into neuron cells. The use of this ability for therapeutic purposes opens great possibilities in the therapy of some diseases, such as the Parkinson's disease, Alzheimer's disease or multiple sclerosis-that is neurodegenerative diseases that afflict still more people, as well as for transplantations of vital organs. Another application of this method is substitution of destroyed cells of the heart muscle after a heart attack, correction of cartilaginous cells after inflammations, substitution of parts of bones, or implantation of insulin-producing cells to patients with diabetes. Much is also expected from introduction of this method in the therapy of tumours and diseases affecting the immune system of patients.
The presumption is that, in a short period of time, cells with precisely characterized cell lines will be developed; it will then be possible to use them for one of the purposes stated above. Because there are many ethical problems resulting from the use of embryonic cells, other approaches that would eliminate the use of embryonic cells are being tested. An example could be the use of animal cells with nuclei inserted from human cells. The first country in the world that allowed therapeutic cloning is Great Britain. The term therapeutic cloning means a procedure during which genetic information from another individual is inserted in a fertilized egg. Stem cells that come from such embryos can then be further utilized. The law in Great Britain, as well as in some other countries, does not consider cloning a human being, that is, creating identical individuals.
In the Czech republic, some theoretical and practical problems concerning cloning and cultivation of stem cells on model experimental animals are being researched at several

institutions of the Czech Academy of Sciences (Institute of Molecular Genetics, Prague, Institute of Animal Physiology and Genetics, Liběchov), medical faculties of the Charles University, Motol Hospital, Institute of Clinical and Experimental Medicine of the CAS, Prague and Mendel's University of Agriculture and Forestry in Brno. As a part of the Program for centres of research and development the Centre for cellular therapy and tissue substitutions was founded in the year 2000. This centre has integrated most of the research workers working on this problem in the Czech republic. Still missing are clear legislative limitations necessary for starting research on human embryonic cells and similar to those that have been passed in some countries of the European Union. Preparatory work on the necessary laws has been, however, started and the assumption is that the law regulating this research will be prepared in quite a short period of time.

Recombinant proteins

While the basic hybridom technology has become a part of production technologies of thousands of firms all around the world, the technology involving production of recombinant proteins came into routine use later. However, this is the technology that is currently the fastest developing area of interest, especially in preparation of new medicaments and medical substances. In connection with the hybridom technology and new substances used for diagnostic purposes, it is necessary to overcome the disadvantages of heterogeneity of generally used monoclonal antibodies of the mouse or rat origin. Aside from completely new drugs, there are substances, originally produced, for example, from human blood and used for diagnostic and therapeutic purposes, produced the same way now.
Today, proteins present in the organism only in few copies may be cloned, expressed in heterogeneous host cells, purified and characterized. Using targeted induction of mutation it is possible to introduce specific changes convenient for clinical and industrial application.
Production of recombinant proteins consists of several steps:

- preparation of DNA constructs (the discovery and widespread use of the PCR techniques was essential)
- insertion of productive organisms, for example bacteria, yeast plants, insect cells and some types of mammal cells
- cultivation of selected productive organisms in vitro, isolation and purification of produced proteins
- insertion of embryonic cells and preparation of transgenic organisms (animals, plants)

All these steps are already performed at a series of research establishments of the Czech Academy of Sciences (Institute of Molecular Genetics, Institute of Microbiology, Institute of Experimental Botany, Institute of Entomology and some research groups at colleges in the Czech republic and at some departmental institutions). Although these are mostly academic institutions, the projects carried out here focus on practical problems. In most cases there is no connection to potential producers in the Czech republic.

Genetically modified organisms (GMO, transgenic organisms) are organisms, into which, using the methods of genetic engineering, a heterogeneous piece of DNA is inserted. This is done in such a way that enables expression of the appropriate characteristic coded by this piece of DNA in the new acceptor. Most cases of GMO can be found among bacteria where this technology started. Genetically modified bacteria are used in the synthesis of recombinant proteins in a similar way to transgenic animals and plant. From the point of view of practical applications, the use of these methods for the development of transgenic plants is essential. The main goal, at the same time, is to increase and improve production and to eliminate the losses caused by weeds and pests. The existing methods of using chemical sprays are not only

financially demanding, but they also pollute the environment with toxic substances (pesticides, herbicides, fungicides). The biggest group of transgenic plants, therefore, consists of plants resistant to insect pests, plants resistant to bacterial, viral and mould diseases. Transgenic plants will, in a near future, help to solve problems not directly concerned with agriculture. If we are able to insert genes carrying resistance into the genome of plants, nothing can prevent us to apply the same method with many other genes. As an example, there are plants prepared this way that produce a structure able to induce an immunity response against widespread infections. These vaccines may be applied to potential recipients in food. Synthesis and application of such prepared vaccines is significantly cheaper. Transgenic plants may be used in the synthesis of a series of other substances. Among these there is, worth mentioning, a very prospective approach in the synthesis of antibodies.
The main goal of gene modifications in animals is improvement of the health state of livestock, improvement of production properties and improvement of digestibility and utilization of feed. Similarly to transgenic plants, there are transgenic animals prepared in this sector as well. They will serve as a source of active substances. Genes of these active substances, which may be acquired, for example, from milk, will be inserted to the genoms of such individuals. Some research establishments, especially the Institute of Molecular Genetics and the Department of Animal Physiology and Genetics of the CAS and at the Research Institute of Animal Production, have mastered the technology of preparation of transgenic animals. In cooperation with research workers of these institutes, transgenic organisms have already been prepared experimentally for planned as well as for practical purposes of production.
Since January 1, 2001, there is a law now in force in the Czech republic regarding manipulation with GMO; it regulates problems of laboratory manipulation with GMO and problems regarding introduction of GMO onto the market. Similarly to other European countries, this law, based on irrational concerns, essentially limits both research and practical use of GMO and food prepared from them. This is happening in the time when the whole world is being flooded by similar products coming from countries whose legislation better reflects advantages and dangers of this technology.

Vaccines

The effect of vaccination on the state of health of the human population is enormous. Perhaps only provision of clean, non-infectious water had larger effect on health state of people than the effects of preventive vaccination against a number of infectious diseases. During the last 200 years, vaccination has helped to eliminate 9 of the most serious diseases of the mankind. Nevertheless, preparation of efficient vaccinations is one of the main goals of medical research. As in many other areas of biology, the use of recombinant-DNA technology in preparation of vaccines has started to be used. It opens a variety of possibilities in areas where classic approaches have not yet succeeded. First of all, it is the problem of infectious and parasitic diseases. Using this technique, it is possible to define a structure of the infectious agents inducing the immune response in the recipient. In order to induce the immune response in this case, it is enough to use just this part of bacteria or virus and it is not necessary any more to be working with all the infectious material. It is not only much more effective, but also much safer. Completely new possibilities are being introduced in the area of preparation of anti-tumour vaccines. Here it will also be first used on tumours of the viral origin. Encouraging results have been acquired in this field in the Czech republic. In cooperation with research workers of the Institute of Haematology and Blood Transfusion in Prague, Institute of Molecular Biology of Plants of the CAS in České Budějovice, and the Institute of experimental Botany of the CAS in Prague a project dealing with preparation of a vaccine

against the papilloma virus 16, the etiologic factor in the development of the cervical carcinoma, is being carried out. The vaccination should become a part of eatable parts of some fruits (tomato, carrot, potato). The goal is to produce a protein in genetically modified fruits given above that would have both a prophylactic and a therapeutic activity.

Current situation in the Czech republic in applied research and application of biotechnological approach and production

In various lists of research organizations and private companies we can find hundreds of institutions and firms claiming that biotechnology is one of their business activities. After a closer look into their program, however, we find out that only a minimum of them is focused on modern biotechnology. Concerning private companies, 90% or even more are represented by distribution companies that only import foreign products on the Czech market.
As stated above, many institutes of the Czech Academy of Sciences and research establishments of universities work on typical projects of applied research supported by financial grants; the goal of these is to develop new medicaments or new diagnostic sets (Institute of Organic Chemistry and Biochemistry, Institute of Macromolecular Chemistry of the CAS, Institute of Nuclear Physics of the CAS, Institute of Molecular Biology of the CAS, Institute of Molecular Genetics of the CAS or institutes of the CAS and the Jihočeská University in České Budějovice). In some cases remarkable results have been accomplished. Among these there is the synthesis of completely new derivates of cytokine analogs showing various inhibitory effects upon the growth of tumour cells that was performed at the Institute of Experimental Biology of the CAS. Most of the plans of institutes of the Ministry of Health, the Ministry of Education and the Ministry of Agriculture cover various spheres of applied research dealing with problems of modern biotechnology. Lately, some programs announced by the Ministry of Industry and Commerce enable companies to receive financial support for development in this field. A big problem is, however, that all this research is almost not at all connected to the possibilities and capabilities of companies operating in the Czech republic. Therefore, it often happens that some very interesting ideas either do not even approach the stage of their practical application or they are applied outside the Czech republic.
As a consequence of these well-known facts, applied research is very little developed in the Czech republic. In the sphere of modern biotechnology this type of research is performed, apart from the institutes of the CAS and the universities already stated above, at some departmental research institutes (Research Institute of Plant Production in Prague-Ruzyň, Research Institute of Veterinary Medicine, Brno, Research Institute of Animal Production, Prague-Uhříněves) and scarcely in some private companies. As an example, we can mention Generi Biotech, Ltd. (molecular genetics), Biopharm, PLC (transgenic animals), EXBIO Prague, PLC, Biovendor, PLC (monoclonal antibodies) and scarcely some other ones.

Application of biotechnological approaches and production in the Czech republic

The biggest problem today is the missing attachment between the plans of advanced research and the plans of production companies. A long series of interesting project end up, at the maximum, by being published or patented. It happens very scarcely that it become clear from the very beginning that new technology or a new product will have a particular producer in the Czech republic, who is awaiting such an application and is ready to start its production quickly. This situation is reflected by a very low number of companies using modern biotechnology. As to bigger companies that survived the process of economic transformation, we can mention Galena-IVAX, PLC, Léčiva, PLC, Pliva-Lachema Brno, PLC, Dyntec, Ltd., BioPharm, PLC, Spofa, PLC. Some others have currently problems and they are turning into

rather distribution companies of their foreign owners. The development of small companies, such as GeneAge Technologies, Ltd (production of recombinant proteins, DNA chips), GeneriBiotech, Ltd (production of oligonucleotides, research in genetic therapy), Top-bio, Ltd Prague, (production or reagencies for amplification of the DNA), rEcoli, Ltd, Prague (production of recombinant proteins), Biovendor, PLC, Brno, EXBIO Prague, PLC, Clonstar, Ltd. (development of new hybridoms, production of monoclonal antibodies), Immunotech, PLC (the biggest producer of ELISA kits in the Czech republic with its own research and production of monoclonal antibodies) is promising. Next to these there are some bigger or smaller companies using fermentation technology in preparation of active substances for various applications, for example Contipro, PLC, Lonza, Ltd., Biocel, PLC.
Although there are, especially at universities, many research projects dealing with problems of application of biotechnological approaches in elimination of toxic wastes, the number of subjects that would bring these to practice is very low. It is possible to mention especially Enrisan-Gem, Ltd., which is doing successful business in this field beyond the boarders of the Czech republic. It is the only company that works on its own research, works on development projects and production of bacterial cultures with hydrolytic activities. Many other companies, such as Aquatest Prague, Geonova, Ltd., Ecoconal, Ltd., Dekonta, PLC, Bioasan, Ltd., G-servis, Ltd, KAP, PLC, Everstar Šumperk, Bioprospect Prague, either import raw materials and prepare final solutions to be used or they only supply foreign products and, at the maximum, perform analysis. To certain extent, we can also mention other companies producing diagnostic sets based on products which were developed using methods of modern biotechnology, although the technologies are not directly used by these companies. These are SevaPharma, PLC, Vidia, Ltd., Itest, Ltd., Test-Line, Ltd.
This overview makes clear the fact that application of results coming from research and development in modern biotechnology is the weakest point in the Czech republic. Development of new drugs based on modern biotechnology basically does not exist. The beginning of work supported by risk investments in the company of I.Q.A., Ltd., Prague (cooperation with research workers from the University in Olomouc) and development of new medicaments at the Institute of Nuclear Research Řež, PLC which, in cooperation with research establishment of the Czech Academy of Sciences, works on some research projects, is promising.

Suggestions concerning further development

In developed countries, support of biotechnology receives extra-ordinary attention. A material of the European Union "The European Research Area: An Emerging Reality" ranks biotechnology, genomics and bioinformatics first, i.e. areas of interest which should receive the most attention. Similarly, in the preparation of the 6th general program these areas were placed among the 6 main topics that should receive the biggest support in the following years. A similar proclamation has not been stated clearly in the Czech republic yet. This is true not only on the state level, but also on the level of individual departments, such as the Czech Academy of Sciences, colleges or ministries. It is, therefore, necessary to make an essential decision that would set appropriate conditions for the development of this field.
The first precondition is to have enough qualified research workers. That means not only in science and research but also in fast growing small and middle-size companies which would apply new information in practice. This requires expansion of capacities of biological faculties, which prepare most professionals in the field of modern biotechnology. This also requires making changes in schedules of some colleges (chemical, agricultural) including the need to intensify teaching molecular genetics to medical students. This requires an improvement in the quality of teaching and introduction of new teaching programs (e.g.

bachelor's degree in this field) in order to prepare highly-qualified professionals for laboratories and to the process of application in production. When preparing the schedules for college students and doctorate students, it would be useful to cooperate with companies potentially applying this research in the Czech republic. This cooperation should not involve only problems concerning classic applied industrial research but also so-called research for education purposes.

Research and Development

In the area of non-oriented research, it is necessary to expand research capacities at universities and at the Academy of Sciences in theoretical fields which provide basis for modern biotechnology, especially molecular biology and genetics. This requires setting up conditions needed to establish new institutions, departments and institutes; conditions needed to enrol new young research workers, especially the talented ones, not only from the Czech republic and to provide appropriate working environment and living conditions for them. The need to create stimulating environment (including the process of legislation) in order to speed up the transfer of potentially interesting pieces of knowledge to practice through both the departmental research organisations and direct transfer to production companies. Constant emphasis on increased efficiency and quality should become an integrated part of all these arrangements. Interdepartmental evaluation of results of research organisations should create the basis for dynamic promotion or suppression of activities of individual subject. Finances, which would be saved this way, should be then used to expand high-quality projects and to establish completely new institutions (including new organizational structures).
To make sure, both in advanced research, especially in applied research carried out at the Czech Academy of Sciences and in plans of departmental research institutions working under the Ministry of Health, Ministry of Agriculture, and the Ministry of Environment, that modern biotechnology is involved is one of the main subjects of their research activities. To make sure that the topics of research works are formulated together with the potential users or companies applying this research in the Czech republic.
Main topics of modern biotechnology can be summarized, in a simple way, as follows:

- development of new medicaments (biggest investments and highest expectations), pieces of knowledge obtained from investigation of the human genome and gradual investigation of genomes of pathogenic bacteria leading to identification of potentially interesting proteins, preparation of monoclonal antibodies against them, in preparation of humanised varieties of these antibodies, in preparation of transgenic animals and plants to ensure the production of both antibodies and proteins for therapeutic use
- development of new diagnostic sets (not only for human medicine)
- development of new genetically modified food, livestock and plants
- development of new ways and approaches in improvement of the environment and elimination of its pollution

In the Czech republic an opinion is being spread out that development of new medicaments is a costly matter requiring financial support that can be provided by only a small percentage of the biggest international corporations. The real situation, however, is completely different. Small companies all over the world are founded with the only purpose to develop often only one new medicament (using the already mentioned methods of modern biotechnology). Their budgets are in the amounts of millions or in tens of millions of collars at the maximum. Experience with risk investments in the Czech republic shows that there are enough of these financial resources but there is lack of really good ideas or projects. The quality of results of applied research is lacking behind; as stated above, there are enough financial resources for

good-quality projects in our country. As we have learned from the USA, introduction of new products to production including complicated clinical testing is provided by newly founded small companies. And then only a very small part of new products, which have the chance to become widely used, become objects of interest of large corporations. Our neighbours in Germany have already realized this and made such steps, with the help of the government, that enabled foundation of a series of similar small companies.

Application

One of the feelings brought from the last conference BIO 2001 (San Diego, June 2001) is that not only production, but basically the whole field of biotechnology in the USA, is performed mostly by private companies. Universities carry out basic research (molecular biology and genetics, immunology, cell physiology and pathology, virology and others). As soon as there is some discovery made that could become an object of production and successful business, it is patented and usually undergoes further development, testing and in cases it succeeds, it is then applied in new private companies founded by the researchers themselves. This approach is probably the basic piece of advice on how to develop the field of biotechnology in our country. The elements of further development should include all types of support provided to new companies applying all the clever ideas that come out as results of our research teams. Foundation of companies that are able to apply modern biotechnology and to take part in international cooperation (mostly within the EU).
State support, in accordance with the main priorities set up by the EU, should provide conditions that would focus projects of newly developing companies or companies already existing onto the main areas of modern biotechnology as stated above.