Biotechnology in Poland

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The contribution to the Conference on "The Other Face of Biotechnology" and its introductory part on Perspectives of Biotechnology require reaching a consensus what biotechnology means. The term "biotechnology" means different things to different people. Some view biotechnology as all forms of biological research, be it cheesemaking and brewing or recombinant DNA (rDNA) technology. Others, only view biotechnology as a set of modern biological techniques (e.g., rDNA, hybridoma technology, and monoclonal antibodies). Some people have analogized biotechnology to a set of new tools in the biologist's tool box by referring to "biotechnologies". To Wall Street financiers and venture capitalists who invested in the creation of companies in this area, biotechnology represents a hot new source of financial risk and opportunity.

In 1984, U.S. Office of Technological Assessments (OTA) arrived at two definitions of biotechnology. The first definition — broad in scope — described biotechnology as any technique that uses living organisms (or parts of organisms) to make or modify products, to improve plants or animals, or to develop microorganisms for specific uses. This definition encompassed both new biological

tools as well as ancient uses of selecting organisms for improving agriculture, animal husbandry, or brewing. **A second, narrower definition refers only to "new" biotechnology: the industrial use of rDNA, cell fusion, and novel bioprocessing techniques. It is the development and uses of the new biotechnology that has captured the imagination of scientists, financiers, policymakers, journalists, and the public** (1).

This last definition implies industrial application of rDNA, cell fusion and novel bioprocessing techniques. In this respect, biotechnologically based therapeutics, including gene therapy, recently quoted among Frontiers in Biotechnology (2), can be hardly considered as "industrial use of synthetic genes". It is safer and more convenient to discuss biotechnology as a set of techniques accelerating, by means of modern methods developed within molecular biology, production of new or already known materials and services of commercial value, so far inaccessible in meaningful quantities or extent. In that sense it is the fast and feasible commercialization of scientific achievements which brought biotechnology to the focus of governments, policymakers, and the public.

With great respect for the classical Biotechnology, which has long and good tradition in Poland, I arbitrarily select the definition of New Biotechnology as a basis for discussion during this Symposium, because the revolution brought by discoveries in fundamental biological research led us to discuss Biotechnology in the context of Public Perception, Intellectual Property, Biosafety and Biodegradation, Protection of Intellectual Property, and other headlines of this Symposium.

Major events which brought commercialization of Biotechnology are as follows:

Major Events in the Commercialization of Biotechnology
(U.S.A, G.B., Japan, Germany) (3)

1973	First cloning of a gene.
1974	Recombinant DNA (rDNA) experiments first discussed in a public forum (Gordon Conference). First hybridoma created.
1976	First firm to exploit rDNA technology founded in the United States (Genentech). Genetic Manipulation Advisory Group started in the United Kingdom.
1980	Diamond v. Chakrabarty — U.S. Supreme Court rules that micro-organisms can be patented. Cohen/Boyer patent issue on the technique for the construction of rDNA. United Kingdom targets biotechnology for research and development (Spinks' report). Federal Republic of Germany targets biotechnology for R&D (Leistungsplan). Initial public offering by Genentech sets Wall Street record for fastest price per share increase ($35 to $89 in 20 minutes).

1981	First monoclonal antibody diagnostic kits approved for use in the United States. First automated gene synthesizer marketed. Japan targets biotechnology (Ministry of International Trade and Technology declares 1981, "The Year of Biotechnology"). Initial public offering by Cetus sets Wall Street record for the largest amount of money raised in an initial public offering ($ 115 milion). Over 80 new biotechnology firms formed by the end of the year.
1982	First rDNA animal vaccine (for calibacillosis) approved for use in Europe. First rDNA pharmaceutical product (human insulin) approved for use in the United States and the United Kingdom.
1983	First expression of a plant gene in a plant of a different species. New biotechnology firms raise $500 million in U.S. public markets.
1984	California Assembly passes resolution establishing the creation of a task force on biotechnology. Two years later, a guide clarifying the regulatory procedures for biotechnology is published.
1985	Advanced Genetic Sciences, Inc. receives first experimental use permit issued by EPA for small-scale environmental release of a genetically altered organism (strains *P. syringae* and *P. fluorescens* from which the gene for ice-nucleation protein had been deleted).
1986	Coordinated Framework for the Regulation of Biotechnology published by Office of Science and Technology Policy. Technology Transfer Act of 1986 provides expanded rights for companies to commercialize government-sponsored research.
1987	U.S. Patent and Trademark Office announces that nonhuman animals are patentable subject matter. October 19th — Dow Jones Industrial Average plunged a record 508 points. Initial public offerings in biotechnology-based companies virtually cease for 2 years.
1988	NIH establishes program to map the human genome. First U.S. patent on an animal — transgenic mouse engineered to contain cancer genes.
1989	Bioremediation gains attention, as microbe-enhanced fertilizers are used to battle *Exxon Valdez* oil spill. Court in Federal Republic of Germany stops construction of a test plant for producing genetically engineered human insulin. Gen-Probe is first U.S. biotechnology company to be purchased by Japanese company (Chugai Pharmaceuticals).
1990	FDA approves recombinant renin, an enzyme used to produce cheese; first bioengineered food additive to be approved in the United States. Federal Republic of Germany enacts Gene Law to govern use of Biotechnology. Hoffman-LaRoche (Basel, Switzerland) announces intent to purchase a majority interest in Genentech. Mycogen becomes first company to begin large-scale testing of genetically engineered biopesticide, following EPA approval. First approval of human gene therapy clinical trial.
1991	Biotechnology companies sell $17,7 bilion in new stock, the highest 5-month total in history. Chiron Corp. acquires Cetus Corp. for $660 million in the largest merger yet between two biotechnology companies.

These major events include discoveries, legal actions, and the response of business world to the new opportunities created by achievements in fundamental research. Also, the above compilation indicates some biotechnological products in the context of governmental actions and financial responses.

What are the types of Biotechnology Products in Development?

According to a 1990 US Pharmaceutical Manufacturers Association (4) survey of biotechnology products in development, PMA member companies had over 100 new biotechnology-derived drugs and vaccines in human clinical testing. Many of the products are still being developed by numerous companies, and they can be placed in several defined categories. Research continues on several of the already approved products, including erythropoietin, tissue plasminogen activator, growth hormone, and interferons. A brief description of the other types of products in development is presented below.

Seven different **Colony Stimulating Factors** are being developed to treat white blood cell disorders including: some cancers, AIDS, aplastic anemia, bone marrow transplants, neutropenia (a condition characterized by a decrease in the number of neutrophilic leukocytes in the blood), and thermal injury. These products stimulate bone marrow to increase blood cell production and restore white cell counts.

Two companies are competing in the development of **Superoxide Dismutase** indicated for the treatment of conditions related to myocardial infraction and renal transplantation, as well as to oxygen toxicity in premature infants.

Hemophiliacs lack the blood clotting protein **Factor VIII** and are susceptible to severe, life-threatening internal bleeding. Factor VIII can be genetically engineered, resulting in a pure protein in sufficient quantities for treatment. Two companies have applications submitted to the Food and Drug Administration (FDA) and are awaiting final marketing approval.

Growth Factors regulate cell proliferation, function, and differentiation. There are several different types of growth factors that are involved in different cellular processes and operate in distinct cells. Several growth factors, including epidermal growth factor, transforming growth factor, fibroblast growth factor, and insulin-like growth factor, are being developed by companies to treat a variety of conditions. Growth factors have many potential uses, including wound healing and the treatment of diabetes, growth disorders, ulcers, wounds, and transplants.

Interleukin is a natural substance that seems to have a wide potential variety of uses but is poorly understood. Interleukins appear to be useful in treating disorders of the immune system. Seven companies have one form of Interleukin or another in clinical testing. Recently, Cetus'Proleukin (interleukin-2) New Drug Application (IND) was turned down by FDA. FDA requested more information and additional testing to determine subsets of kidney cancer patients who will benefit from Proleukin treatment. Many of the indications for which interleukins are being tested have no alternative treatment, and thus interleukin, while mechanistically poorly understood, is the only potential therapeutic treatment.

Monoclonal antibodies are protein molecules produced by white blood cells that can recognize and target foreign matter (antigens) in the cells. As such, they are able to target the delivery of drugs to particular cells on the basis of antigen recognition. One monoclonal antibody-based therapeutic, Ortho's Orthoclone OKT-3, is available on the market for treatment of kidney transplant rejection. Eighteen companies have other monoclonal antibody-based therapeutics in clinical trials for a variety of indications, including treatment of graft-host disease, cancer and septic shock, as well as prevention of blood clots, pseudomonas infections, rheumatoid arthritis, and diabetes. Centocor's Centoxin and Xoma's Xomen-E5 are both awaiting approval for the treatment of septic shock, and the two companies are already engaged in a patent dispute. A large market is anticipated for these two products in particular. As with interferons and interleukins, the market potential for monoclonal antibodies is promising but somewhat unclear.

Three companies are testing **Tumor Necrosis Factor** (TNF) for the treatment of cancer, and all are in early stages of clinical testing. TNF is a cellular messenger involved in the triggering of immune defenses. It damages tumor-related blood vessels and interferes with the blood supply and nourishment of the tumor. Again, research continues in efforts to determine exact mechanisms of action, and market potential at this point is relatively unknown as efficacy studies are being in progress.

Research and early clinical testing on **Recombinant Soluble CD4s** for the treatment of AIDS are being conducted by several companies. CD4s are cell surface receptors believed to be involved with the AIDS virus' (HIV) cell surface binding. Research concentrates on creating an analog to the naturally occurring CD4s receptor that will bind to HIV and prevent it from binding to the cell receptor, thus inactivating the virus. CD4 research represents just one use of biotechnology in AIDS research.

Vaccine research has been greatly enhanced with the advent of biotechnology. Biotechnology allows for the design and production of subunit vaccines, which are much safer than conventional vaccines that incorporate the actual virus. Subunit vaccines are developed from the viral protein coat, which by itself is incapable of reproducing and infecting the patient. Two vaccines for Hapatitis-B are available on the market, and testing being done on a variety of potential AIDS, malaria, and herpes vaccines. The market for these vaccines is very large, and if safe and effective vaccines are produced, their manufacturers should be richly rewarded by a most-welcoming marketplace.

Several other products are in early clinical testing as well. The market potential for many of the drugs described is very large. Infectious disease, cancer, and AIDS all lack effective conventional treatments. If the mechanism of action and the function of the naturally occurring proteins being studied for use as therapeutics are further delineated, a realistic market and demand can be estimated. Right now, some of the products being developed are being pulled by the market, while others are more research driven and their com-

mercial potential is difficult to evaluate as further scientific understanding is still needed.

Since the title proposed by the Chairman of the Conference on "The other face of Biotechnology" for my talk was "Polish Biotechnology", let me say a few words about Poland and about the status of Biotechnology in Poland. Poland's population is above 38 millions of inhabitants. Over 30% of population are under 18 and almost 60% are in the working age which is 18 ÷ 64 for men and 18 ÷ 59 for women. More than 10% of Poles are in post-retirement age. Out of those who are over 15 years old, 40% have only primary education, 25% secondary education, 7% are university graduates. Over 60% of the population live in towns, most of which are small and medium size. According to U.N. classification, Poland is a country at a medium level of development. A pattern of Gross Domestic Product (45% industry, 10% construction, 9% agriculture) reveals an underdevelopment of services. The country is a leading supplier of coal, lignite and copper, and the world's second largest producer of rye and potatoes, and sixth largest producer of sugar beets and milk. But the efficiency of agriculture, dominated by small farms, is not high. Per hectare, yields of basic cereals and sugar beets are low, in spite of relatively high consumption of mineral fertilizers and good saturation of farms with machinery. Employment in agriculture and forestry accounts for more than 27% of the economy's total product. Agriculture contributes more than 14% to the country GNP.

Recognizing the importance of Biotechnology for economy and well-being society, the Committee of Biochemistry and Biophysics of the Polish Academy Of Sciences, headed by the member of the Polish Academy of Sciences, Professor W. Ostrowski, elaborated and published in 1984 the **"Report on Biotechnology in Poland"** (5); as a consequence, two National Programs, sponsored by the State Committee for Research and Development and the Polish Academy of Sciences, had been established. Two Polish eminent scientists, Prof. K.L. Wierzchowski and Prof. J. Pawełkiewicz, headed the programs on **"Molecular Basis of Biotechnology"** and **"Molecular Biology and Genetic Engineering of Plants"**, respectively. These two Programs lasted 5 years, from 1986 to 1990, and coordinated and financially supported the research of over a hundred of research groups from universities, industrial research laboratories, and institutes of the Polish Academy of Sciences, involved in the studies on organization and function of genetic apparatus of microorganisms and yeast, genetics and molecular biology of microorganisms, applications of molecular biology methods in human genetics, chemical basis of genetic and enzymatic engineering, introduction of biotechnology for health protection, low molecular regulators of cell metabolism, genetic engineering of plants, and others. In the program coordinated by Professor Pawełkiewicz molecular backgrounds in plant biotechnology, such as Molecular Studies of Plant Biotechnology, Plant Protein Biosynthesis and Pre-ribosome Mechanisms were the major headlines with the specific subject, such as tRNA and tRNA-genes, synthetases and protein biosynthesis with particular

attention to phosphorylation, ribosomal RNA and small rRNA structure/function correlation, analysis of structure of rRNA by means of metal ions, nitrogen fixation process, induction of proteins during protein fixation. Independently, some other programs, such as the National Program of Combating Cancer Diseases, generated research on the technology of poly– and monoclonal antibodies. These five years programs blossomed in numerous (ca 1000) scientific papers published mostly in journals of international circulation. Product oriented projects ended-up with:

— technology for five drugs: Bioglobulin, Histoglobin, Protalbin, Lactid and Stimulovac,

— technology of vaccine against Pertussis,

— technology of immunodiagnostics for HSV, Rubella and HBV,

— hybridization tests for PSTV and PLRV (potato viroids),

— laboratory — scale technology of ^{32}P-labelled nucleoside triphosphates.

The implementation of molecular biology techniques was possible due to the development of effective methods of synthesis of oligodeoxyribonucleotides and oligoribonucleotides and an easy access to oligonucleotides enabled the synthesis of genes, which after cloning and expression in *E. coli* made accessible such proteins like human αTNF and its muteins, recproinsulin, several antigens of HIV-1 (gp120, gp17, gp24, gp41), protein C, protein pre-S1 of HBV, antigen gD of HSV-1, pro-substance P. Cloning and expression techniques were also successfully used for preparation of streptokinase and streptodornase. In the same way, *E. coli* bacteria overproducing such enzymes as DNA Klenow Polimerase 1 and two restriction enzymes, Fok1 and MboII, were obtained.

Unfortunately, the economy of the State was lacking of any reasonable system solution of the problem of Technology Transfer. The sick economy was not imposing any pressure for innovation and competitiveness on the industry. Instead of improvements and scale-up efforts for domestic technologies, home industry preferred to purchase foreign technologies. The comparison of some data from the discussed above events on the commercialization of biotechnology in the leading countries in the world with some facts from Poland seems to be very illustrative: recombinant human insulin was approved for use in U.S. and United Kingdom in 1982, while the first recombinant protein in Poland, hαTNF, was obtained on Laboratory scale in 1987 (6), four years after deciphering of TNF gene by Belgian investigators. This indicates that the delay of Polish Molecular Biology in comparison to the USA was ca 10 years. Also, the list of our achievements clearly indicates that Molecular Biology in Poland is chasing the world leaders and, more general, reflects the unsatisfactory level of biological sciences in Poland, so literaly expressed by M. Laskowski (7). On the other hand, this list speaks strongly for the fact that educational function of aforementioned programs has been fulfilled.

As a consequence of the Polish political and economic transformation since 1989, Poland changed its attitude to Research and Development. New **State**

Committee of Scientific Research cancelled all programs and started the policy of granting individual research projects.

The body of 29 members, selected in way of Democratic Election, decides with the help of nominated specialists and advisers, serving as peer-reviewers, about the excellency of submitted research projects, parallely distributing the financial resources to the state-owned Institutes according to the position of a given institute on the ranking list of scientific excellency.

In my personal opinion, the primary sin of the State Committee of Scientific Research, was the lack of scientific policy, which is most important for the development of the country. Regretfully, in the official State document calling for this new Committee, the term "Biotechnology" does not exist, which reflects the attitude to Biotechnology in this country. One of the presumptions was that privatized industry, forced for competitiveness, has to generate the need for new biotechnologies. On the other hand, the decrease in Gross National Product, lowered the financing of Science. Research and Development to the year's verge of 0,6% of GNI. This economic situation of today is reflected, among others, in a number of students (1200 for 100 000 population). For comparison, in South Korea this figure is 3 times higher. However, it would be unfair to say that in this time of poor economy science has observed only loses: selected Centers of Excellency, such as the Institute of Bioorganic Chemistry PAS, the Institute of Biochemistry and Biophysics PAS, the Institute of Experimental Biology PAS, the Center of Microbiology and Virusology PAS, the leading institutions in Poland carrying out an active research in biological and pro-biotechnological fields, got the new settlements and financial support for renewal of major pieces of scientific equipment.

We believe that this selective policy of development of Centers of Excellency complies with the postulates of Committee of Biotechnology of the Polish Academy of Sciences, which in 1991 elaborated the document demanding the creation of Centers of Excellency in Biology, Chemistry and Biochemistry, and Medicine, which would focus their research on:

— molecular biology, molecular genetics, cell biology, immunology, bacteriology, virusology,

— enzymology, protein and enzymatic engineering, bioprocess engineering,

— molecular diagnostics, immunodiagnostics, immunopreventive agents, therapeutics, antisense strategy.

The Committee of Biotechnology also proposed the creation of the National Agency for Biotechnology, and the concentration of research and development efforts on the following topics:

Molecular basis for Biotechnology:

— biochemical and genetic regulations of gene expression and metabolic pathways in microorganisms of importance for biotechnology,

— biochemical and genetic basis for plant nitrogen fixation,

— molecular basis of interactions between plants and pathogens for generation of ecologically safe methods of plant protection,

— engineering of proteins and peptides for the potential use in human and weterinary prophylactics, therapy and diagnostics,

— engineering of proteins for their use in chemical industry.

Biotechnological Sources of Energy:

— utilization of lignocelluloses by means of microorganisms, immobilized bacteria and immobilized enzymes,

— biomass conversion into industrial ethanol.

Biotechnology for Ecological Protection and Food Production:

— molecular structure and organization of genetic apparatus of selected plants and animals, identification, isolation, cloning and characteristics of selected genes,

— control of genetic expression of selected plants and animals,

— molecular basis of nitrogen fixation,

— genetic transformations of plant and animal cells,

— bioenergetics and understanding of molecular mechanisms of photosynthesis.

Biotechnology for Health Protection:

— cell fusion and rDNA technology for production of the new generation of therapeutics, immunoprophylactics and diagnostics,

— molecular probes for genetically controlled diseases,

— new generation of therapeutics based on the concept of antisense-mRNA strategy,

— monoclonal antibodies and their utilization in diagnostics and delivery of therapeutics.

Besides that, the Committee of Biotechnology suggested creation of the National Depository of Microorganisms and postulated the novelization of our Patent Law in order to make it compatible with Western legislation.

We may notice with satisfaction that within the structure of the State Committee Scientific Research the **Subcommittee on Molecular Biology and Biotechnology** has been created in 1992. The list of granted projects published in Bulletins of the State Committee of Scientific Research, is elusive, since projects related to Biotechnology are compartmentalized in several subcommittees, but at first glance it seems that majority of research groups contributing to former programs are financially supported. Also new projects, aiming at the production of transgenic animals (fish, rabbit) and transgenic plants are among those which are granted; but the data to which extent it follows the suggestions of concentration of research on New Biotechnology are yet illegible.

The analysis of the list of research projects granted by the State Committee for Scientific Research, as well as inventory "Who is Who in Polish Biotechnology", done by the Chairman of this Symposium, Dr. T. Twardowski (8), indicate that ca. 1000 scientists declared themselves as biotechnologists, but critical evaluation indicates that 100 teams are involved in New Biotechnology in Poland. This number is positively verified and confirmed by statistics that ca. 70 research teams are customers in the Laboratory of Oligonucleotide

Synthesis, producing oligonucleotides used as hybridization probes, PCR primers, gene components, e.t.c.

In my personal opinion the major factor which hampers the development of science in Poland is poor financial status of scientists. An average monthly salary for a research associate with Ph.D. degree is on the level of 250 USD or lower, which is ca. 10 times less than that in the USA. Therefore, our country suffers from the brain drain process to the extent not comparable to that at any former period of our post-war history. Our best students or Ph.Ds without difficulty find jobs outside Poland.

But let me make, on this occasion, a somewhat bitter comment. From my personal experience, out of my 20 former Ph.D. students or distinguished collaborators 7 are working in the USA as professors, group leaders or senior scientists, but only 2 of them are Associate Professors in Poland. My experience is not unique. Assuming that the education of one Ph.D. costs 200 000 USD, the calculation is very simple but depressive; Poland is not getting any support from the West — it is just a reversed process — Poland is strongly and painfully contributing to the Western science. The message directed to our Government is the following: as long as the income level in Poland is not equivalent to the qualifications, Poland will not be able to develop high-technology industries, including New Biotechnology. It is the human factor and brain potential which are the major factors which influence the well-being of mankind. The global economy may present spectacular achievements, which, unfortunately, are far away from the fair geographical distribution. The history of our civilization noticed numerous examples of this phenomenon.

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Biotechnologia w Polsce

Streszczenie

W artykule przedstawiono definicje biotechnologii oraz osiągnięcia „nowoczesnej biotechnologii, która jest podmiotem artykułu. Nakreślono stan ekonomiczny nauki polskiej, a na tym tle biotechnologii i nauk probiotechnologicznych. Zaproponowano kierunki rozwoju biotechnologii w Polsce.

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