Review Article

Medical Biotechnology: Problems and Prospects in Bangladesh

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Abstract

Biotechnology is the knowledge and techniques of developing and using biological systems for deriving special products and services. The age-old technology took a new turn with the advent of recombinant DNA techniques, and boosted by the development of other molecular biological techniques, cell culture techniques and bioinformatics. Medical biotechnology is the major thrust area of biotechnology. It has brought revolutions in medicine – quick methods for diagnosing diseases, generation of new drugs and vaccines, completely novel approach of treatment are only a few to mention. The industrial and financial bulk of the industry mushroomed very rapidly in the last three decades, led by the USA and western advanced nations. Asian countries like China, India, South Korea, Taiwan and Singapore joined late, but advancing forward in a big way. In all the Asian countries governments supported the initiatives of the expert and entrepreneur community, and invested heavily in its development. Bangladesh has got great potential in developing biotechnology and reaping its fruits. However, lack of commitment and patriotism, and too much corruption and irresponsibility in political and bureaucratic establishment are the major hindrance to the development of biotechnology in Bangladesh.

Key words: *Biotechnology, Bioinformatics, Recombinant DNA technology*

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Introduction

The central theme of biotechnology is using biological systems, an organism or any part of it, for derivation of special products or services to satisfy human need. A major part of the knowledge and discipline involves developing the organism or an appropriate part of it for the purpose, generating the product and processing. The origin of the technology is often traced to making yogurt by using bacteria or fermenting beer by yeast.

Before 1970s, the methods for getting a better organism were limited to searching among natural variants, selective breeding, hybridization, and induced mutation by chemical and physical agents. Despite some significant successes, this traditional biotechnology was not a well-known scientific discipline.

However, the nature of biotechnology was changed forever when Stanley Cohen and Herbert Boyer invented the recombinant DNA technology (also called molecular biotechnology, genetic engineering, gene cloning, gene splicing or gene transplantation) in 1973. DNA or Deoxyribonucleic Acid is at the root of all inherited characteristics of an organism. DNA contains the genes - functional units of heredity each bearing a message of hereditary characteristic. The above scientists invented methods of recombining genes from different sources, thus producing "Genetically Engineered" (GE) or "Genetically Modified" (GM) organisms with newer characteristics.[1]

The recombinant DNA technology essentially involves:

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1. Identifying a gene (unit of inheritance) with desirable characteristic in one organism.
2. Isolate the gene
3. Introduce the gene to and express the characteristic in another organism[1-4]

Before the advent of the above technology genetic materials of two organisms could be combined almost exclusively through sexual reproduction, which was possible only within a species and between closely related species or genera. Cross or hybridization, that is, sexual union crossing the species boundary, often resulted in sterile offspring. By hybridization technique it was impossible to combine genes, say of, rice and carrot, tomato and cow, etc. The molecular biotechnology or genetic engineering opened up the possibility of transferring characteristics of one organism to another, irrespective of their relationship, that is, a bacterial characteristic to a plant or even a human characteristic to a bacterium could be transferred by transferring one's gene to the other.

Along with the development of recombinant DNA technology other molecular biological techniques as sequencing, DNA synthesis, gene expression regulation, monoclonal antibody production, cell culture and stem cell differentiation, aided by bioinformatics - hybrid off shoot of biotechnology with modern computing device, have brought revolutions in medicine: developed quick methods for diagnosing infection or monitoring cholesterol levels, generated series of new drugs, vaccines, and completely novel classes of therapeutic agents, forced breakthroughs in understanding diseases as diverse as cystic fibrosis and cancer. Yet the progress so far is considered by many scientists as only a beginning. Within the next two decades, scientists foresee individualized targeted therapies, development of predictive technologies leading to a new era in disease prevention, diagnosis, and treatment.[4-10] An overview of the subdivisions and scope of biochemistry is illustrated in Figure 1.

What follows next is a very brief review of the fields of modern biotechnology in prevention, diagnosis and treatment of human diseases; followed by the global picture with particular emphasis to the Asian countries; and prospects, problems of its development and possible strategies of solution in Bangladesh.

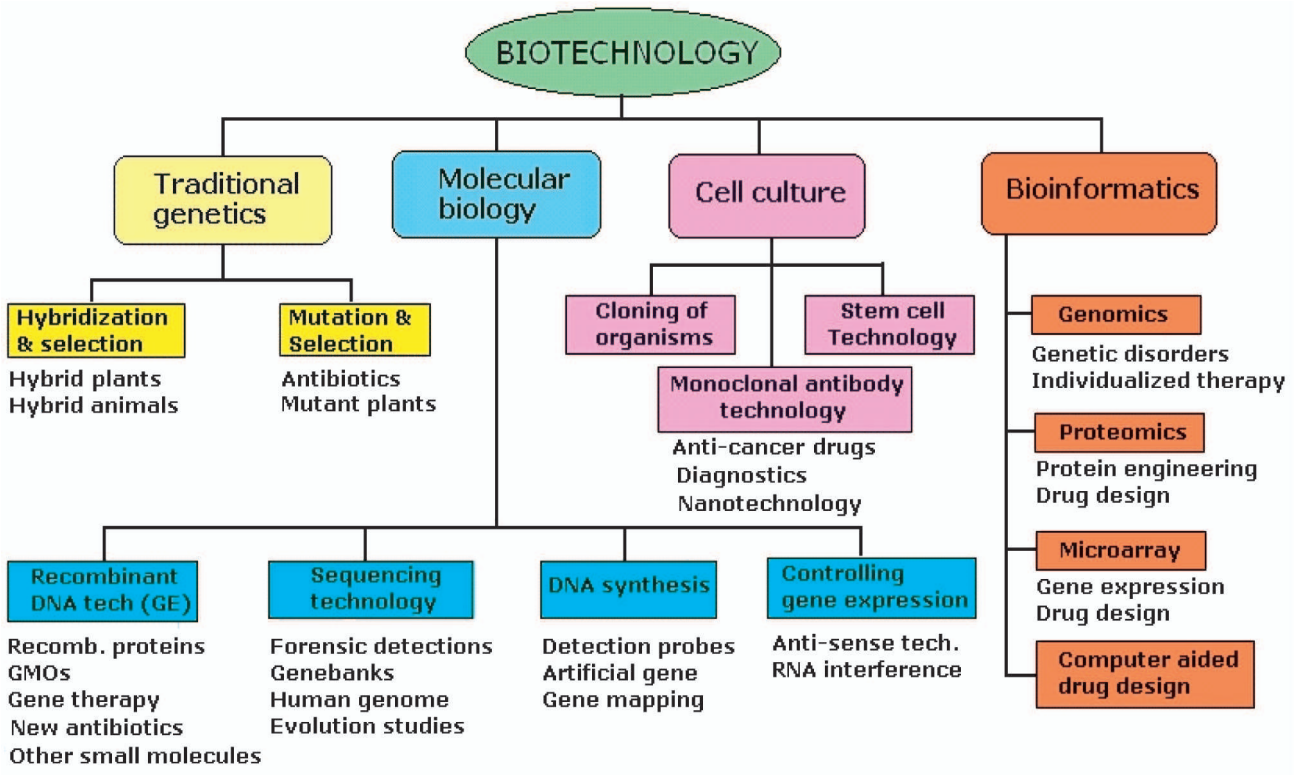

Fig 1. Major sub-divisions of Biotechnology and some of their products and services

Biotechnology in prevention, diagnosis and treatment

Production of recombinant proteins

Therapeutic proteins

Before the 1980s proteins were rarely used as drugs. Exceptions were insulin and various vaccines. With the advent of genetic modification, however, human proteins have become available in huge quantities.

The first "bioengineered" drug, a recombinant form of human insulin, was approved by the U.S. Food and Drug Administration (FDA) in 1982.[11] Until then, insulin was obtained from a limited supply of beef or pork pancreas tissue. By inserting the human gene for insulin into bacteria, scientists were able to achieve bacterial production of large quantities of the life-saving protein. In the near future, patients with diabetes may be able to inhale insulin, eliminating the need for injections. Recombinant DNA products include, human serum albumin, human insulin, interferons, growth hormone, erythropoietin, etc.[12-16]

Human proteins produced by recombinant DNA have several advantages. They are indistinguishable from their authentic human counterparts but are safer as they are less likely to be contaminated by infectious agents, and they can be produced in large quantities. A case in point is human growth hormone, which previously could only be obtained from human cadavers and carried the risk of Creutzfeld-Jakob disease (CJD).[17]

Biotech vaccines

Biotechnology also plays an important role in preventing disease. Vaccines produced by recombinant DNA methods are generally safer than traditional vaccines because they contain isolated viral or bacterial proteins, as opposed to killed or weakened disease-causing agents. However, many citizens in developing nations do not have access to any vaccines, let alone ones derived from biotechnology.

In conventional vaccine production, the pathogen of interest is grown in the laboratory, collected and either killed or severely weakened before being injected into humans. The immune system then produces antibodies against the vaccine, protecting the body against future infection. If a fragment of the microbial DNA is used as an alternative vaccine, this will produce the antigenic protein directly in the body and may induce the immune system to produce antibodies. DNA vaccines may be safer than conventional ones. They may also be easier to manufacture and may be stable at room temperature. These traits would greatly facilitate development and distribution of vaccines in the developing world. [18-25]

The first recombinant vaccine, approved in 1986, was produced by slipping a gene fragment from the hepatitis B virus into yeast. The fragment was translated by the yeast's genetic machinery into an antigen, a protein found on the surface of the virus that stimulates the immune response. This avoided the need to extract the antigen from the serum of people infected with hepatitis B. [20-21]

Because of their efficiency, safety, and relatively low cost, recombinant vaccines may have particular relevance for combating long-standing diseases of developing countries, including leishmaniasis (a tropical infection causing fever and lesions) and malaria.

Plants as bioreactor

Plants are being used as bioreactors for the biosynthesis of products with biotechnological interest. Plants have the ability to generate complex recombinant proteins with desired structures, maintaining biological functions. Transgenic plants can produce properly folded proteins at low costs and in large amount. Researchers have already demonstrated that recombinant proteins made in plants have similar biological activity as those produced in mammalian, yeast or bacterial cell culture. Plants also offer greater safety because they do not harbor mammalian pathogens or microbial toxins. Moreover, a handful of candidates are already into human clinical trials, where initial results have shown efficacy and safety.[26-35]

In addition to their use as bioreactors, plants can be used as potential delivery systems for oral vaccines. Edible biotherapeutics (edible vaccines), are very intriguing example. Currently, most vaccines require cold storage and professional administration through injection. Therefore, researchers are working on genetically engineered plants to deliver vaccines through food. The cost of plant-derived, orally administered hepatitis B vaccine is estimated to be

one-sixth of the cost of current hepatitis B vaccines. Enough antigen to immunize all babies in the world each year could be grown on approximately 80 hectares of land. Plant-derived antimalarial vaccines are also in trial.[36-42] Moreover, plant tissues provide protection and prevent degradation of the antigen when it passes through the gut.[43-44]

Transgenic animals

By the early 1980s, scientists were able to insert DNA from humans into mice and other animals. Because they now express human genes, "transgenic" animals can be studied as models for the development of diabetes, atherosclerosis, and Alzheimer's disease. They also can generate large quantities of potentially therapeutic human proteins. For example, a recombinant "clot-buster," expressed in the milk of transgenic goats, currently is being tested in patients.[45-55]

Gene therapy

Unlike conventional treatments, which attempt to deal with the consequences of a defect, gene therapy aims to correct the defect itself. In order to function, the therapeutic gene must reach the nucleus of the target cell. Various vectors have been used to achieve this, of which viruses were the first to be investigated. These have a natural ability to enter a cell and become active.

Current gene therapy systems suffer from the inherent difficulties of effective pharmaceutical processing and development, and the chance of reversion of an engineered mutant to the wild type. Potential immunogenicity of viral vectors involved in gene delivery is also problematic.[56-57] To address this issue, nanotechnological tools in human gene therapy have been tested and nanoparticle-based nonviral vectors (usully in size) in transportation of plasmid DNA described. Therefore, successful introduction of less immunogenic nanosize gene carriers as a substitution of the disputed viral vectors seems beneficial in repairing or replacing impaired genes in human.[58-60]

Whatever the vector, there are two methods by which gene therapy can be carried out: 1. in vivo gene therapy, in which the vector is injected into the body and has to find its way to the target tissue 2. ex vivo in which a sample of tissue is taken from the patient, treated with the vector and then replaced.[61]

Currently active trials of gene therapy are going on over such varied diseases cystic fibrosis, vein graft rejection, psychiatric disorders, inner ear developmental anomalies, brain tumors, mitochondrial genetic diseases.[61-69]

The use of viruses to deliver genes has shown risks to human health, making trials with these viruses controversial. Another method involves the use of liposomes, hollow membranous spheres which encapsulate the gene. Liposomes fuse with the cell membrane, releasing their gene into the cytoplasm.[66,69]

The convergence of nanotechnology with biotechnology will allow for safer gene delivery methods that are not based on viruses. Chemically synthesized nanoparticles that carry genes or therapeutics specifically to diseased cells are currently being tested in animals.[69]

Antisense technology

In 1978, Paul Zamecnik of Harvard University demonstrated that the DNA to protein mechanism could be interrupted by the use of small synthetic stretches of DNA called oligonucleotides. He used an oligonucleotide with a sequence complementary to an mRNA molecule needed by a particular virus to reproduce itself. The oligonucleotide bound to the mRNA and stopped it moving onto the ribosome for translation. Early work is in progress to develop antisense technology as specific DNA drugs against cancer, viral infection and Crohn's disease (an inflammatory condition of the bowel).[70-91]

Polymerase chain reaction (PCR)

Biotechnology also has dramatically improved diagnostic capabilities. The polymerase chain reaction, a method for amplifying tiny bits of DNA first described in the mid-1980s, a single segment of gene could be identified, copied, and tested within hours. It has been crucial to the development of blood tests that can quickly determine exposure to the human immunodeficiency virus (HIV), for example. Genetic testing currently is available for many rare disorders, such as hemophilia, which is caused by a mutation in a single gene. Little can be done to prevent or slow some of these diseases, however, and the underpinnings of more complex illnesses such as cancer, heart disease, and mental illness are as yet not well understood.[92-98]

Development of human stem cells

Stem cells are the early-stage cells in an organism that have been shown to give rise to different kinds of tissues. They have successfully replaced or repaired damaged tissue in animal models, and they hold great promise for treating human diseases such as Alzheimer's and diabetes. Although the vast majority of people agree that cloning to produce humans (reproductive cloning) is unacceptable, therapeutic cloning, in which the cloning process is used only to harvest stem cells, is hotly debated. Therapeutic cloning could supply stem cells that exactly match a patient, minimizing the serious risks associated with tissue rejection.[99-107]

Monoclonal antibodies

The development of monoclonal antibodies in 1975 led to a similar medical revolution. Cesar Milstein and George Kohler won the Nobel Prize in 1984 for inventing a technique that produced the first monoclonal antibodies. The body normally produces a wide range of antibodies—immune system proteins—that root out microorganisms and other foreign invaders. By fusing antibody-producing cells with myeloma cells, scientists were able to generate antibodies that would, like "magic bullets," hone in on specific targets including unique markers, called antigens, on the surfaces of inflammatory cells.

Soon after their invention in 1970's the monoclonal antibodies (mAbs) earned the reputation of 'magic bullet,' in particular against tumor specific antigens and infectious diseases.[108] The molecular biological techniques augmented both its accuracy and versatility.[109] Present antibody based therapeutics include unconjugated mAbs, antibody drug conjugates (ADC1), antibody based radioconjugates (ARC), bispecific antibodies (BsAb) recognizing two different antigens, Ab fragments and Fc fusion proteins.[110-112]

Antibodies and antibody fragments can be relatively easily modified by molecular biological techniques.[113-116]

Bioinformatics

With the help of bioinformatics— powerful computer programs capable of analyzing billions of bits of genomic sequence data— scientists are cracking the genetic codes to use the information for achieving various medical goals. For example by analyzing the codes of bacteria and discovering "weak spots" vulnerable to attack by compounds identified via high-throughput screening. This kind of work led in 2000 to the approval of Zyvox, the first entirely new antibiotic to reach the market in 35 years.[117-128]

Genomics and sequencing of human genome

The sequencing of the human genome, completed just three years ago, also has given scientists an incredibly rich "parts list" with which to better understand why and how disease happens. In the foreseeable future not only will every human gene will be identified, but the factors controlling their expression will also be known. This knowledge will unlock new targets for diagnosis, treatment and prevention of disease. It will change medicine forever, allowing treatments to become increasingly tailored to the specific needs of the individual.[129-137]

Proteomics

Proteomics is about analyzing the complete set of expressed proteins in a given cell,[138] the path was open to understand emergent properties that result from the complex interactions of metabolic and regulatory networks.

The technical cornerstone of proteomics is the high throughput mass-spectrometry-based identification and quantification of proteins.[139] Proteomics is being used to unravel protein constellation of the cell, virulence factors, deranged host proteins, host-pathogen interactions, identification of microorganisms, characteristics of genes and genomes, and also for designing drugs against diseases including cancer, cardiovascular and infectious diseases. Using technologies such as mass spectrometry can detect protein biomarkers in the blood that may indicate early signs of disease, even before symptoms appear. One such marker is C-reactive protein, an indicator of inflammatory changes in blood vessel walls that presage atherosclerosis.[140-157]

Microarray technology

The automation of biochemical binding assays in small chips called microarrays enables scientists to screen thousands of chemical compounds for their effectiveness against disease-causing proteins in a very short time. This high-throughput screening, as it is called, would not have been possible without years of serious investment in basic biotechnology research.

A microarray is a two-dimensional arrangement of specific biological probes (e.g., DNA or protein molecules) deposited in an addressable fashion on a glass slide or other substrates (e.g., polymer-coated glass, plastics, nitrocellulose). The size of the glass slide is usually one by three inches, with thousands of isolated biological probes ranging from 50 to 300μm in diameter arrayed on the surface. Deoxyribonucleic acid (DNA), protein,[158-160] cell[161-163] and tissue microarrays[164-165] also called biochip microarrays, have helped understanding gene and protein functions. Microarrays can also be used for disease diagnosis, prediction, prevention, and drug discovery.[166-169]

Computer aided drug design

Computer aided drug design is the use of omputational techniques to find out the characteristics of an appropriate drug molecule. Often a single molecule, for example a protein from a pathogen creates the whole range of disease features; or sometimes abnormal host molecules are the reasons behind the disease. In such cases the strategy to combat the disease is to introduce a new molecule that binds and inactivates the causative molecule. Traditionally almost blind search was performed among myriads of natural or synthetic substances. Computer aided drug design or rational drug design has cut the cost and time of drug search by several orders of magnitude. Today it is possible to select candidate drug molecules from huge available databases and check whether it can bind to the active site of the troublesome molecule using computational docking procedures.[117,170-195]

Nano-biotechnology

Nano-biotechnology or nanomedicine is another rapidly moving field. Nanosensors are being developed from particles that are about 50,000 times smaller than the diameter of human hair to detect protein and gene expression in individual cells in the body, thus allowing the assessment of the health of cells at early stages of disease. Scientists are developing a wide variety of nanoparticles and nanodevices, scarcely a millionth of an inch in diameter, to improve detection of cancer, boost immune responses, repair damaged tissue, and thwart atherosclerosis.

Nano-biotechnology can develop powerful diagnostic tools for the isolation and diagnosis of various diseases.[196-197] Drugs can be delivered as nanoparticles to targeted sites, including locations that cannot be easily reached by standard drugs.[198-201] Many agents, which cannot be administered orally due to their poor bioavailability, can be delivered with the help of nanotechnology.[202-204] Nano-formulations protect drugs from degradation or denaturation and prolong half-life.[183-184] Nanotechnology can be applied to deliver antigens for vaccination.[205-209]

Global picture of biotechnology with emphasis to the Asian countries

According to the global accounting firm Ernst & Young the total biotechnology industry revenues were about US$ 25 billion in 2000. Then it was predicted that it would be US$ 50 billion in 2010. But the reality exceeded the prediction. By 2005 the total revenue exceeded US$ 63 billion mark. Estimated global biotech industry revenues for publicly-held companies reached at $83.6 billion for 2011, up from $80.6 billion in 2010. Analysts at Morgan Stanley Research estimate that 7 of the 20 best-selling drugs in the U.S. during 2010 were biotech drugs. Biotech drugs represent an estimated 10% of the total global prescription drugs market, and about 20% of the U.S. prescription market.[210]

In all Asian countries, the governments are the ones driving biotech research. Private industry's role, in comparison, is miniscule. This is mainly because biotech research requires large investments in infrastructure and has a high cash-burn rate, while the returns in the initial years are quite low. Strong research-focused private players are rapidly emerging in countries such as China[211-212], India[213-216], Taiwan[217-219], South Korea[221-222], and Singapore.[222-224]

China forayed into biotech with a focus on plant genomics and transgenic technology. It was the only country from Asia that participated in the human genome project and is now shoring up its genome sequencing capability to facilitate the sequencing of microbial genomes. India was amongst the front runners in biotechnology initiatives in agriculture and now there is an increasing interest in the field of medical biotechnology from the private sector with quite a few players.[211-212]

The government of India has established the Department of Biotechnology under the Ministry of

Science and Technology, with huge budget to boost the advancement of biotechnology. The Government of India also took collaborative programs with UNESCO to establish the Regional Centre for research, training and education in biotechnology under the auspices of UNESCO. India is already being globally recognized as a manufacturer of economical, high-quality bulk drugs and formulations. With a huge base of talented, skilled and cost-competitive manpower, and a well-developed scientific infrastructure, it has great potential to become a leading global player in biotechnology.[214-215]

In India the biotech industry has been growing at a double-digit rate over the last five years. The industry size stood at $4 billion for financial year 2010-11. Indian biopharmaceutical industry constitutes 60% of the biotech industry and grew at 21% to reach $2.3 billion in 2010-11. Vaccines, insulin, erythropoietin and monoclonal antibodies have been the mainstay of the biopharmaceuticals segment.[216]

Taiwan's medical bio-technology industry began in 1984 with government funding qualified laboratories to run recombinant DNA technology experiments. Today, it has plans for a number of investment projects including science-based industrial parks, research incentives and a combination of public and private funding. [217-219]

South Korea, for example, has identified four key sectors for development and growth, namely, genetic engineering, proteomics, bioinformatics and disease treatments. [221-222] Singapore, too, has identified four key areas for structural improvement and better links between researchers and industry. It has perhaps a more coherent strategy than most others, with a very strong national planning.[222-224]

Applications in medical biotechnology are the more lucrative option for Asian countries, but this has high entry barriers and investment needs. With Asia's emergence as a preferred manufacturing base for bulk drugs and pharmaceutical dosage forms, and clinical development; it would be a move up the value chain for these players to extend these capabilities in chemistry into biology. The potential is furthered by the biopharmaceutical industry's rich research pipeline and greater expected therapeutic efficacy of clinical candidates for current lifestyle diseases.

About $126 billion worth of branded drugs are to go off-patent in the next 5 years, (from June 2012). While innovation is essential for sustainable long-term success, generic markets and services sector offers robust growth prospects. Asian firms can be expected to gain a strong foothold in the world generics markets given their strong chemistry and reverse engineering skills.

Challenges for Bangladesh

Biotechnology in general and Medical Biotechnology in particular is definitely a very prospective area of development for developing countries like Bangladesh, as the example of India shows. In Bangladesh although some biotechno-logical work and industrial initiatives in the traditional sense of the term has been taken, the field of modern medical biotechnology is still untouched. Only a few successful attempts has only been taken by international institutions in Bangladesh as ICDDRB. The national institutions are yet to prove their capabilities and potentials.

A summary analysis of the situation in Bangladesh is given in the form of SWOT analysis below.

SWOT analysis of Bangladesh

Strengths

Rich biodiversity

Low cost of labor in research, development and manufacturing

Fairly trained human resource

Weakness

Lack of commitment and patriotism, and too much corruption and irresponsibility on part of the political and bureaucratic establishment are the major weaknesses regarding development of the country in general, and biotechnology in particular.

Emigration of the experts to rich countries

Unawareness on part of entrepreneur community

Disinterest in investing in research and development (R & D) by the national entrepreneurs

Weak connection to the knowledge and information network

Almost total absence of coordination between research and industry

Poor coordination between national research institutes and resources

Lack of venture capital

Opportunities

Fairly large local market

Big export potential

Scopes for contract research

Threats

Heavy investments by neighboring countries like India and China

Anti-biotech propaganda, fueled by traditionalism and extreme 'environmentalism'

Unfavorable intellectual property right (IPR) and trade policies imposed by the rich and technologically advanced countries or their representative agencies like World Bank and IMF.

Concluding remarks

Biotechnology has the potential to provide more and healthier foods, reduce dependence on fossil fuels, offers more effective cures, diagnosis and prevention of diseases. It could be a shining path for industrial and economic development through generation of products and services both for domestic consumption and export.

The weaknesses on part of Bangladesh as noted above are addressable. However, the government must be the supporter and major investor in this effort, as the initial phase of development involves good amount of investment which would give only a delayed and diffused return, which the private sector is incapable to undertake.

The most optimistic feature of this fledgling technology and the industry is that:

1. It is not as capital intensive as other industries like chemical, automobile, electronic industries, etc.
2. In contrast it is more knowledge intensive, where intelligent people in a country like Bangladesh have got a fair advantage.
3. Small modular ventures could be taken by many entrepreneurs at a time, who may later form conglomerates at an appropriate time.
4. The know-how of the state of the art technology is still within reach of us. It has not advanced too far yet. Thus there is fair possibility that Bangladesh could get hold of it with an all out dash.

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