Growth of biotechnology in India

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After a period of sustained support from the Government of India for over 15 years, R&D in biotechnology and life sciences has come of age. Some of the real products have just reached the marketplace. India has just crossed the lag phase and is at the beginning of the log phase of growth in this sector. This is the time when the private sector should come forward and catalyse investments in a big way. Global business can only be one of the objectives of biotechnology. This technology has a great scope to contribute directly to alleviation of human suffering.

Biotechnology has kindled the imagination of a lot of people globally and India is no exception. It may be of interest to trace the growth of biotechnology and to make an assessment as to where we are at the present juncture. At the outset, I want to state that my assessment is essentially a qualitative one. Quantitative assessment in terms of total investments, returns in each segment, market size, social costs, etc. would need separate research and perhaps have taken up a few years down the line when the commercial output would have grown significantly. I have also avoided mentioning the names of individual institutions and companies involved. There has been extensive research in the country on a variety of biotechnologies, but this review is confined to definitive leads towards end-products.

In retrospect, the Government of India should be complimented for taking the initiative to create the National Biotechnology Board (NBTB) in the Department of Science and Technology (DST) in 1981/82. NBTB graduated into a full-fledged Department of Biotechnology (DBT) in 1986. These initiatives have been vital for the growth of biotechnology in India. With CSIR, ICMR, DAE, ICAR and DRDO also joining the fray, the growth of biotechnology in the country is essentially due to government support. The private sector has been making periodic background noises in terms of investments in the recent past, and one hopes this will become a decipherable language in the future.

Quality of science

Biotechnology is a knowledge-based industry and, therefore, the quality of science behind the R&D efforts is important. In terms of modern biotechnology based on hard-core molecular biology, including recombinant DNA manipulations, structural biology of macromolecules, cell and developmental biology, bioinformatics, downstream processing, there were hardly any groups in the country in the late 1970s, with expertise in these areas. In a span of 20 years the country has built around 150 groups (a group is defined to consist of a leader with about a dozen associates) with expertise in these areas. These groups are publishing good scientific papers in modern biology in international journals of high impact, if not all the time in *Nature* and *Science* (this is my personal view), although the total number of publications may not have changed. This is perhaps a welcome development in the context of an overall decline in the total number of science publications in the country[1,2]. A detailed analysis is warranted. The problem is that these 150 good research groups are located in about two dozen agency institutions (CSIR, DBT, DST, DAE, etc.) and a dozen universities including the Indian Institute of Science (IISc). It is depressing that in a country with about 250 universities, hardly a dozen universities qualify to be centres of major R & D in the area of biotechnology. A serious introspection is needed and the issues involved are complex.

The DBT has invested substantially in building the infrastructure to carry out R& D in life sciences in the country[3]. It has created and supported new centres and institutions in different parts of the country in a wide spectrum of subjects ranging from immunology to neurosciences. The DST has also chipped in with supporting some of the major institutional facilities and basic research. The interesting feature of all this support is that it is largely extra-mural. This means that the support has gone beyond the DBT and DST institutes to creating infrastructure and research competence in other agency (e.g. CSIR, ICAR) laboratories and universities. The concept of extra-mural research support practised by all government funding agencies in India is vital for the growth of science beyond their own institutions, and has made networking in research possible. Initial experience with networking different institutions was not good, but the country has come a long way since then. Today, almost all mega projects involve the participation of multiple institutions. At the same time, there is also scope for smaller, single investigator-based projects.

Systems biology approach[4]

While scientists in the country have by and large followed the hypothesis-driven gene-by-gene approach, where a few proteins/genes involved in a metabolic pathway are studied in great detail, the era of genomics has ushered in the systems biology approach. Knowledge of the human and other genome sequences has led to technologies such as DNA microarray and other adjunct methodologies, which enable identification of a basket of genes directly or indirectly or remotely involved with say, a disease process. Thus, for example, at least 200 genes are implicated in type II diabetes. Similarly, proteomics, pharmacogenomics, metabolomics, etc. convey a mega-scale protein/gene-based analysis of drug responses, metabolic pathways, etc. The advantage of the first bottom-up approach is a thorough understanding of the proteins/genes involved in limited reaction steps. The second top-down systems biology approach gives a handle to genes/proteins that may even be remotely regulating a biological process and may have never

been implicated using the gene-by-gene approach. However, many of the large number of genes identified in the second approach, may all be coding for hypothetical proteins (of unknown function), which would call for the first approach to identify the function. Both the approaches have to feed into each other, the end objective being to come up with a small set of genes/proteins that can become drug targets, diagnostic and vaccine candidates or useful transgenes in agriculture or industrial microbiology.

Diagnostics

The whole of 1990s was a learning experience. The early emphasis was on the development of reagents/kits for disease diagnosis. The emphasis on molecular diagnostics stemmed not only from its relevance, but also from the fact that products have to be developed in quick time to justify government funding. Thus, competence building and product development were taken up side-by-side. Many laboratories developed reagents/kits for molecular diagnosis of diseases (e.g. malaria, tuberculosis, typhoid, filaria, etc.). MOUs were signed with companies for production, and this step itself was considered as a great achievement. But, not a single indigenous diagnostic kit reached the market. Scientists found that laboratory marvels do not necessarily perform in the field. Companies realized that they need to do something more than putting a nice wrapper and marketing the product.

The new millennium has been different. Indigenous diagnostic kits, not just assembled kits with imported reagents, have indeed hit the market (Table 1). Many more are in the pipeline. More importantly, scientists and entrepreneurs have learnt at least some lessons. They are prepared to work together to develop a product. We do have a new brand of scientist-turned entrepreneurs. This makes a significant difference for the growth of this knowledge-based industry. It will take some more time for the indigenous diagnostic sector to make an impact in a market filled with imported reagents and assembled kits. There are hardly one or two companies making polyclonal and monoclonal antibodies on a commercial scale, that is so vital for ELISA-based diagnostic kits. At present, most of the hospitals/research institutions/companies import such antibodies at exorbitant costs. A positive beginning has, however, been made in the field of molecular diagnostic-kit manufacture. There are issues facing the industry that need to be addressed. It took more than four years of struggle to make NACO (National Aids Control Organization, Health Ministry) to let indigenous entrepreneurs make a bid for the supply of HIV diagnostic kits. Often, grants and loans from external agencies carry stipulations that systematically eliminate the budding entrepreneurs of this country. But, a day will come when the indigenous kits will replace import, with one brand name or another. India can also supply kits to other developing countries. Some efforts in terms of hardware development will also help the indigenous entrepreneurs. Import of say polycarbonate matrices, on which the reagents are coated, will attract duty, but the import of the whole diagnostic kit as such may escape duty, in the name of its use for the alleviation of human suffering! It is always tempting to be a trader than an entrepreneur!

Table 1. Indigenous diagnostics

Disease	Technique	Status
HIV	Agglutination ELISA Western blot	Commercial
Hepatitis C	ELISA	Commercial
Cysticercosis	ELISA	Commercial
Tuberculosis	PCR	Development
Leishmania	PCR	Development
Malaria	ELISA/ DIPSTICK	Development
HLA	PCR/ELISA	Development
Typhoid	ELISA	Development

Many other diagnostic kits are in the pipeline. Commercial molecular diagnostic services are now available in a few centres.

Vaccines

The manufacture of recombinant hepatitis-B vaccine by a couple of companies at Hyderabad has made international impact. This is, perhaps, the first commercial recombinant product produced in India. This has led to a ten-fold fall in the price of this vaccine and is likely to go down further. It has also led to confidence in taking up manufacture of other biopharmaceuticals, recombinant or otherwise. Under the Jai Vigyan Mission of the Prime Minister, cholera, rabies, tuberculosis, malaria, HIV and Japanese encephalitis virus have been taken up for vaccine development by DBT[3]. A dozen institutions and three or four industries are involved in this effort. ICMR also has a major interest in modern vaccine development. Negotiations for international collaboration for HIV vaccine development are also underway by the DBT and ICMR (Table 2). Other biopharmaceuticals such as insulin, streptokinase, interferons, lysostaphin, etc. are in the pipeline. There is also good scope to modernize the conventional animal and poultry vaccines. It is, however, a matter of regret that a major effort towards development of anti-fertility vaccines in humans never saw the light of the day. Many companies involved in the manufacture of conventional human vaccines (DPT, MMR, etc.) are undergoing modernization. Investments have been made to improve infrastructure, enhance production capacities and adhere to GMP guidelines. The companies are also investing in relevant basic research and tie-up with academic institutions.

I believe India should aim for a global leadership in vaccine manufacture. This is, perhaps, the cheapest mode of protecting the health of our people and for the same reason does not find favour with multinational companies (MNCs), which do not find vaccine manufacture to be economically viable. In fact, the international health community is concerned that even conventional vaccines such as DPT, MMR, etc. are in short supply and there is discussion as to how to sustain the interest of MNCs to manufacture vaccines for the Third World[5]. Tax breaks, financial support from rich countries, support from philanthropic foundations are all being considered. The problem will aggravate as and when vaccines become available for the major killers – HIV, tuberculosis and malaria. These have to be manufactured on a global scale and supplied to countries with widely different economic standards. This is where India can step in by providing infrastructure, expertise and cost-advantage for global vaccine manufacture. This can also help to address our own health concerns. After all, India is a major market for disease control.

Our companies should also learn basic lessons. For example, a dozen companies

Table 2. Indigenous modern vaccine development

Disease	Vaccine type	Status
Hepatitis B	Recombinant	Commercial
Hepatitis A	Viral vaccine	Development
Rabies	DNA vaccine	Development
Rotavirus	Live vaccine	Development
Anthrax	Recombinant	Development
Jev	Live vaccine/DNA vaccine	Development
Leprosy	Live vaccine	Commercial
HIV	Recombinant/DNA vaccine	Research
TB	Recombinant/DNA vaccine	Research
Malaria	Recombinant	Research
FMDV	DNA vaccine	Research

In addition, interesting leads for vaccines against *Leishmania*, *Pneumococcus* and *H. influenzae B* have been obtained. Biopharmaceuticals such as recombinant streptokinase and interferons have been commercialized. Recombinant insulin is in the pipeline.

have entered into recombinant hepatitis B manufacture and the turnover of each company has plummeted down dramatically, endangering the survival of single product-based companies. This is like all the farmers switching to tomato cultivation, because it sold at Rs 20 per kg last season. The coming season will be a glut for tomatoes and the farmers have to sell it at 20 paise per kg or give it free! There has to be a better planning and strategy. The single-product companies should soon diversify and look for some innovation. The future market will be for combination vaccines. Above all, the companies should practice professional ethics, live and let live, honour the commitment to academic partners and never compromise with the quality of the products. Overall, the feeling is upbeat and India has great potential to move ahead.

Drug manufacture

India has been a major exporter of generic drugs, but our strength has been in the area of cost-effective process development. Our strength has not been in the area of the development of new pharmacophores based on new drug targets. A few (two or three) companies have invested in the genomics/proteomics set-up and, perhaps, there could be random success stories in the long run. But, I do not see the kind of strength I feel, for example, in vaccine or biopharmaceutical R&D. The few success stories we have seen earlier are in terms of licensing molecules developed by modification of known drugs and not in terms of actually bringing a new drug into the market. This is due to a variety of reasons including lack of clinical trial facilities of international standards in the country. Developing new drugs against diseases such as diabetes (type II), cardiovascular, cancer and neurological disorders through molecular target-based approach requires intense research at the level of basic biology, before the vagaries of drug-molecule development can be handled. I am not sure whether Indian companies can handle it. I am aware of only one Indian company that has gone all out to develop molecules for cancer therapy using the target-based approach. Perhaps, there could be a couple of success stories with new drugs for infectious diseases. This area is, however, not a priority for many major pharmaceutical companies. However, the drug sector can still look for cost-effective process development for new pharmacophores under appropriate licensing agreements.

I do see a great possibility for propagating our traditional systems of medicine towards global business. Ayurveda has attracted a lot of attention and Kerala has even made it a tourist attraction. Siddha system, unique to Tamil Nadu, needs to be exploited. These systems do seem to have cures for arthritis, asthma, skin disorders and in general against autoimmune maladies, where the modern allopathic system does not have a real answer. The two major requirements are scientific validation and standardization of preparations. Anecdotal evidence for performance is not enough. It is also a huge task to sift the real remedies from a host of fakes. The New Millennium Initiative (NMITLI) of CSIR in this direction, tying up institutions and industries with traditional and modern scientific backgrounds for authenticating and standardizing specific remedies, can lead to successful results. The ICMR/Health Ministry also has a major interest in this area. Personally, I do feel that the active principle approach is unlikely to succeed, and it would be better to use the concoctions as such, ensuring adequate supply of raw materials without over exploitation. At this stage, however, India lags behind China considerably, which has been able to market Chinese medicines globally.

Agricultural biotechnology

It is indeed clear that India has to keep pace with the ever-increasing population in terms of food production, ensuring quantity and quality. The availability of land is forever shrinking. The so-called adequate levels of food grains at present are, perhaps, due to the segment below the poverty line, not being able to access adequate food. If everyone can afford to eat his/her full quota of food, the production may actually fall short of demand. In any case, genetic manipulation of plants is a sound technical option to increase productivity, both in terms of quantity and quality.

The *Bt* controversy

Activists have done a great disservice to the country by over exploiting and exaggerating concerns of environmental consequences, development of superresistance, monopoly of MNCs, etc. The deliberate mixing up of the so-called terminator gene concept with the *Bt* gene did a lot of damage to the indigenous efforts of scientists, who were also branded as agents of MNCs. Nevertheless, *Bt*-cotton, that has the *Bt* gene to combat major pests and has been successfully grown in the US, China and a few other countries[6,7], is the best bet to make a start in India. After all the delays, the Mahyco–Monsanto product is in the field. Typical of the Indian ethos, there are two versions of the performance of *Bt*-cotton after one season. The company claims it is a success in the five states grown and activists claim it is a failure, in the sense that the yields are no better than the non-*Bt* variety. In the meanwhile, I understand that the farmers are

rushing to buy the clandestine *Bt* seeds introduced by another company, since they are happy with the performance! One report states that there has been a 70% decrease in pesticide spray.

This expectation of increased yield of the *Bt* variety baffles me. *Bt* gene does not have growth-promoting properties. It can only act by protecting against bollworm and, therefore, its performance has to be compared with that of the corresponding non-*Bt* variety only in that context. The saving and benefits have to be in terms of decreased pesticide sprays and lesser exposure of the farmers and the environment to the poisonous chemicals. Above all, in areas of significant bollworm infestation, *Bt*-cotton should provide an insurance against a great loss to the farmer. A systematic analysis of the performance of *Bt*-cotton for a few seasons grown with appropriate monitoring and counselling by experts, is the need of the hour. There has to be some mechanism to ensure that farmers are not duped with spurious seeds. More important would be to mobilize *Bt* genes into local varieties suited to the cotton-growing states. There is significant research on new *Bt* and other genes in public-funded institutions, that could perform even better than the proprietary *cry1Ac* gene and the cotton variety used at present.

Research and development on transgenic plants[8]

In addition to *Bt* genes, significant amount of research in public-funded institutions is being carried out on strategies to combat biotic and abiotic stresses. More than 20 institutions are involved in developing transgenic crops to protect against insect, fungal and virus attacks. Majority of the strategies to protect against insect pests have used *Cry* genes. There are fewer studies with proteinase inhibitor and lectin genes. Studies on transgenics against fungal attacks have used chitinase, b-1,3-glucanase, osmotin and oxalate decarboxylase genes. Coat protein and replicase genes have been used to generate transgenics against viruses. The crops covered are essentially rice, tobacco, cotton, tomato, egg plant, *Brassica*, etc. There have been stray attempts to produce edible vaccines (rabies glycoprotein) or control fruit ripening. Research efforts to develop transgenics against abiotic stresses are more recent in the country and some examples are provided in Table 3.

Development of transgenics to improve nutritive quality of foods is of great relevance to this country. Some of the products under development are listed in Table 4. Potato with balanced protein from amaranth, transgenic rice with b-carotene and iron, oo-mustard with low erucic acid and low glucosinilate, mustard with b-carotene, and tomato with oxalate decarboxylase gene to break down oxalic acid and release minerals are but a few examples that can have a large impact on the quality of nutrition available to the people. Engineering rice to improve nutrition should become a priority. In addition, chloroplast transformation, that can enhance expression potential of the transgene, and also be an answer to the concern of non-target gene transfer through pollen has been successfully achieved.

The *Bt* controversy has generated an element of uncertainty among scientists as to the end goal of their research. The government has to step in with a strong policy to support and encourage these products, and scientists should have a clear road map to take the products to the field. In addition, internationally, public–private partnerships are being negotiated so that the best technology is used without exploitation of the farmer or consumer and with profits to the private sector, a win-win situation for all. One example would be the joint ownership of a transgenic product, where the proprietary gene of a company is introduced into a local variety preferred by the farmers of a region. The ICAR should take a major step and put an end to this bogey of MNC monopoly by aggressively proceeding to put the products developed in public-funded institutions into the field. There is also no harm in striking a deal with the private sector, so that the public–private partnership in agriculture sets a new trend for the benefit of all parties concerned.

There have also been investments in propagating simpler technologies such as tissue culture and micro propagation, biopesticides and biofertilizers. Large-scale demonstration projects have been executed. The impact of all these efforts will be felt only if these measures are taken up by the farmers on a large scale.

Other biotechnologies

There is a whole gamut of areas ranging from environment, animal husbandry, medicinal and aromatic plants, biofuels, aquaculture to commodities such as silk and leather, where the projects have led to development of specific products and strategies. One hopes that some of these would reach the end-user sooner than later. An NIMITLI programme on biotechnology of leather, involving dehairing and processing of leather avoiding the use of toxic chemicals, is making good progress. In all these projects, one sees a focus in taking the strategies to the field and there is hope that at least some of them will fructify sooner than later. A variety of environment biotechnology-related processes ranging from effluent treatment from dye industries, bioremediation of mine soil dumps to development of oil zappers are available through indigenous efforts (Table 5)[9]. Examples of few other unrelated technologies developed are listed in Table 6. All these have good potential and one hopes that they will prove to be viable in the long run.

Post human genome initiatives

India did not participate in the human genome sequencing project. There was

Table 3. Examples of strategies against abiotic stresses

Genes used	Target
*gly*I and *gly*II genes (glyoxylases)	Salinity and metal tolerance
ATPase and Na^+–H^+ antiporter gene	Salt tolerance in rice
Genes of polyamine pathway	Osmotic stress in rice, egg plant
Cod A gene (choline oxidase)	Salt tolerance in *B. juncea*, indica rice
hsp100 and *pdc1* genes	Stress response in rice
Osmotin, Connexin	Abiotic stress in rice, egg plant
Inositol synthase gene	Salt tolerance in rice
Hal I (K^+ transport)	Rice, egg plant

Table 4. Transgenics for improved nutrition

Potato with *Ama*1 gene (balanced protein)
Transgenic mustard for *b*-carotene (oil)
Ferritin iron in rice
Oxalate decarboxylase gene in tomato (release of micronutrients)
oo-transgenic mustard (low erucic and glucosinilate)

Table 5. Environmental biotechnology packages

Bioremediation of mine spoil dumps
Ecological restoration of degraded ecosystems and wastelands
Technology for mangrove afforestation
Biosensors for detection of organophosphorous pesticides
Production of biosurfactants from wastes
Development of bioscrubber for removal of obnoxious odours from industrial emissions
Oil zapper technology for bioremediation of crude oil spills and treatment of oily sludge
Microbial treatment of cassava starch factory wastewater
Chemico-biochemical process for desulphurization of gaseous fuels and emissions
Process for removal of acid dyes, direct dyes and reactive dyes from the spent dye bath

Table 6. Some examples of other applications

Skin cell culture for treatment of burns
Limbal cells for treatment of childhood blindness
Cryo preservation of bone marrow cells
Anti-venom antibodies from chicken eggs
Enzymes for textile and paper industry
Bioleaching for gold extraction

some criticism that India lost an opportunity to be part of this mega exercise. I personally feel that India did not lose anything by not being part of this effort. It was considered much too expensive to get the 'also ran' status. In any case, enormous information is available in the public database for exploitation, and there are enough DNA-sequencing machines in the country attesting to India's competence in DNA or even genome sequencing. I only wish that all these machines are put to optimal use! Some people feel that we should fully sequence at least one organism. I am not sure about its utility. I wonder whether it is like exploding a tiny nuclear device to join an exclusive club!

India has developed its own genome programme, that has extended beyond the human genome programme. Centres were set up to identify and analyse for known and new mutations in major genetic disorders, especially haemoglobinopathies, in the population. This capability is now available only in a few centres in the country, although thousands of tribal families have benefited as per DBT information. It should become a routine practice and be part of genetic counselling. A beginning has been made to offer commercial services in the area of molecular diagnostics. Real time RT–PCR, flow cytometry and other techniques are part of these services to diagnose cancers and infectious diseases. But, these are just a couple of establishments in Mumbai and Delhi, and the country would need much larger number of such diagnostic services. Projects on human biodiversity based on DNA analysis of the ethnic populations in the country have led to interesting information on the patterns of human migration. A major initiative was the setting up of the DNA fingerprinting centre at Hyderabad by the DBT. This has popularized the use of DNA technology in forensic medicine, wild life and biodiversity research in a big way. An interesting aside is that the Commerce Ministry resorted to DNA finger-printing analysis to demonstrate that Indian Basmati rice is different from Pakistani Basmati and, therefore, can command a higher price! The reach of DNA technology is wide.

In the post-genome era, the DBT has invested significantly in areas listed in Table 7. The participation of India in the international rice genome project is significant. Despite rough rice genome drafts being made available by Syngenta, Monsanto and the Chinese, the international effort headed by Japan is considered important and is expected to provide an authenticated and thorough version with adequate coverage that is essential for annotation and synteny studies with other cereals. The contribution made by India in mapping portions of the *Bombyx mori* genome has led to the country being invited to be part of the international silk genome project. Similarly, contributions in the area of the molecular biology of *M. tuberculosis* and the demonstrated strength in structural biology, has led India to become a partner in the international structural genomics programme on this dreadful pathogen. Important legumes such as pigeon pea and chickpea have been earmarked for functional genomics studies. I feel that major studies should also be carried out with millets. Infrastructure has been built to undertake SNP and mutational analysis in the population.

Table 7. Post-genomics era

Structural genomics (*M. tuberculosis*)
Rice genome – chromosome 11
Pigeon pea/chickpea – functional genomics
Cancer genomics
Systemic disorders (diabetes, eye disorders, deafness, etc.)
Neurological disorders
Stem cell research
Bioinformatics

Major initiatives have been undertaken with respect to specific neurological disorders and type II diabetes. The CSIR has mounted a NIMITLI programme on cancer genomics with specific reference to gall bladder, head and neck cancers, and gliomas. A similar initiative has been started with the eye diseases. An underlying objective in these programmes is to develop an indigenous, reusable macrochip (with limited number of genes) to provide comprehensive diagnosis of a given disorder. Thus, one is looking for an indigenous version of a cancer chip, an eye chip, a type II diabetes chip, etc. An interesting NIMITLI programme is on the development of a bioinformatics software with several modules covering functional genomics, proteomics, drug design, pathway engineering, etc. This is ultimately aimed to be user-friendly, platform-independent, cheaper and compete with Axelrys and Tripos software in the market. The DBT has set up close to 60 bioinformatics centres in the country in academic establishments, providing the manpower and infrastructure to undertake the NIMITLI programme, mounted by the CSIR. Specific software for protein identification and prediction have been developed independently. It remains to be seen as to how the indigenously developed software would perform in the market.

An immediate consequence of the post-genome initiative is the creation of expensive infrastructure in terms of DNA

microarrys and systems for proteomics, together with the requirement for confocal and other expensive microscopes and FACS analysis as well as the high throughput systems. While all this infrastructure would help to usher in the systems biology approach, it needs to be realized that product development will still take its own time and there will be demand for newer technical skills.

IPR, bioethics, policy and administrative issues

Everyone is aware that India has to change its patent laws to fall in line with TRIPS agreement before 2005 (ref. 10). While amendments are being taken up in parliament in the agriculture sector regarding registration of plant varieties, biodiversity aspects, farmers' and breeders' rights, similar steps towards product patent, GMO patenting and definition are pending and hopefully will be in place before 2005. The validity of Indian patents has been extended to 20 years through a recent amendment. But, there has to be a visible change in the working of the patent offices and their knowledge base.

Apart from ethical and environmental concerns in the use of transgenics in agriculture, there are also major concerns in germ line gene therapy, stem cell research and even prenatal diagnosis, where the human embryo is the central actor. The government agencies and private groups are quite active in this area in the country. The final policy guidelines are more or less ready and should be available with the ICMR/DBT.

Some policy guidelines are also needed in streamlining the working of GEAC (Genetic Engineering Approval Committee) and DCGI (Drug Controller General of India), when it comes to recombinant products. There is also confusion as to how the approvals for carrying out clinical trials for ayurvedic formulations are to be obtained. India should be setting up the norms in this case, rather than looking up to British Pharmacopea. Ideally, GEAC should be an autonomous body serviced by a government department. The whole philosophy has to be to encourage and support indigenous efforts and provide guidance as to how to plan and handle safety issues. There is no need to exaggerate the safety concerns and there has to be a scientific basis to back up the concerns. It needs to be ensured that uninformed activism against GM technology and the use of animals in research do not retard the progress of this country in this sunrise industry. Public perception and education are important for the progress of biotechnology in the country. Scientists, knowledgeable in the area, should come forward to educate the public and media and counter wild, unauthenticated propaganda against this technology.

The government needs to be complimented for supporting R&D in biotech over the years. Scientists of the country have participated in a big way in formulating the R&D agenda in biotechnology. A reasonable peer-review mechanism is in place in the country to select and approve research projects for funding. While the budget for research in the area of biotechnology keeps increasing every year with all the agencies pitching in, the process of release of funds for the projects leaves much to be desired. This is a general problem. It takes anywhere between three months to and one and a half years to receive grants after a project has been officially approved. The receipt of grants for the second and third years is riddled with problems and the money is invariably received towards the end of a year, and that money is to be spent before March 31 of the following year! There is a great deal of confusion over the Utilization Certificate and Expenditure Statements. The problem lies with the fund-receiving institutions as well. A different process has to be evolved for the receipt and utilization of funds in R&D projects. These projects should be evaluated in terms of technical audit and not just in terms of rendering financial accounts. The fund-release mechanism followed in the NIMITLI programmes of the CSIR is worthy of emulation. It would help if there could be periodic interagency meetings between DBT/ICMR/CSIR/ICAR at the highest level to evolve and execute a master plan and to ensure mutual cooperation.

Biotech education

There is a clamour to start biotech (BT) teaching programmes in the country. A tremendous hype, comparing BT with IT, has led to a plethora of colleges offering M Sc and even B Sc programmes in BT. While the M Sc programmes originally started by the DBT/UGC at the All India level are indeed of good quality, many private colleges and shops are making a quick buck with the biotech and bioinformatics courses. Students have been promised a great future, but many of these institutions have neither the teachers nor the infrastructure to run these programmes. I feel that we are already overproducing M Sc students, looking at the number of candidates going round without gainful employment. In particular, bioinformatics is a specialized programme and needs to be done for 12–15 months, preferably after an M Sc or Ph D level of training. It is a powerful tool, but cannot be a standalone option for any start up in the long run. It needs to have a downstream tie-up with an experimental facility or industry and should be capable of attracting contract projects. Survival on the basis of charging students exhorbitantly will not work beyond a few years. In the meanwhile, engineering colleges have joined the bandwagon and I am not sure as to what kind of products they will be turning out. There is need for a comprehensive review of BT education in the country and an overkill will only spoil the party.

Opportunity for India

In my perception biotech affords opportunities at two levels. One is, of course, to aim for global business. Table 8 lists the areas according to my judgement, where India can compete. The justification for including these areas has been provided in this commentary. In addition, India has adequate expertise, infrastructure and cost advantage to undertake contract projects from international sources. India needs to build up its clinical trial facilities to international standards. This will help our drug/vaccine industries and also provide business opportunities. Since no drug/vaccine can be tested in India, if it is not tested in the country of its origin, the concern about

Table 8. Global business for India

Vaccine manufacture
Traditional medicine/nutraceuticals
Diagnostics/protein pharmaceuticals (internal and developing countries)
Contract projects/clinical trials
Transgenics in agriculture

using India as a 'guinea pig' can be addressed. But, it needs to be ensured that tests are not conducted on the Indian population clandestinely.

Global business can only be a part objective of biotechnology. In my opinion, the major concern has to be to address the health and nutrition concerns of our people. It would be worthwhile to have a specific target. For example, can we set up a 15–20-year programme to use biotech to transform poor, illiterate children suffering from malnutrition into healthy, literate youth of tomorrow? Can the biotech R&D efforts be used to provide a nutritious meal through midday meal programmes in schools? Can transgenic rice/potato/tomato constitute a cost-effective basic component to provide value addition to nutrition with respect to proteins, calories, vitamins (A in particular), micronutrients and iron? Would it be possible to have an immunization programme for these children using combination and stable vaccines to protect them against infectious diseases? Modern vaccine development is a priority for the developing countries[11]. Such a programme would need the expertise and participation of various groups from different scientific disciplines, NGOs, government and industry. I feel that a national mission in this direction would justify all the biotech efforts and investments in the country. A road map needs to be prepared.

Finally, India has to go a long way to innovate and make value addition to the various biotech sectors. While such efforts are underway, the successes so far have been with products known for a long time in the developed world. Start-up companies and young entrepreneurs need financial help and support for longer periods. Once again, it is the government that has come up with financial support for R&D in industries. The DBT supports research foundations and has also come up with a proposal to support R&D in industry. The NIMITLI programme of the CSIR is another initiative. The Technology Development Board and the Drug Research Development Group of the DST are the other examples. But, genuine venture capital from the private sector is lacking. Some of the venture capitalists are no better than moneylenders. Biotech industry needs longer and sustained support and cannot give returns in two or three years. Associations, federations and confederations governing Indian industries would do well to go beyond organizing annual conferences and summit meets and constitute study groups to undertake in-depth studies on potential areas and catalyse investments in a big way. If I can hazard a guess, the government (all agencies put together) has perhaps invested Rs 1500 crores in the last 15 years in biotechnology in terms of direct costs for creating infrastructure (including new institutions) and R&D support. It is projected that the biotech business will be around 5 billion dollars (I do not know how these numbers are arrived at). In all these projections, substantial emphasis is given to genomics, proteomics, stem cell research and bioinformatics as major contributors. I feel that we need to be careful on these assessments. None of these will be money spinners in the immediate future. For example, the hype on stem cell application is giving rise to realities of complexities involved in directing the stem cells to a particular lineage. Reports such as 'stem cells not so stealthy after all'[12] or 'show us the cells'[13] highlight that one has to go a long way to realize the applications. This is true of the other mega areas as well. Quite often, the hype is created to sell hardware. None of this analysis is meant to dampen the enthusiasm to get into these areas. At this stage all these have to be treated as research explorations only. There is much hope on the bioinformatics approach as a major commercial activity. It is too early to predict its growth in India. The success would depend upon attracting major contract projects from international pharmaceutical companies. The other option is that these efforts are tied up with downstream users in the country or abroad. I am not sure as to how many companies will use this approach within the country.

In my perception, India has just crossed the lag phase of the biotech growth curve and has entered the log phase. It is at this stage that one needs all the support and investments for accelerated growth of the industry. The biotech future will be challenging and exciting. To me, it will be worth all the effort if it can contribute at least to some extent, to the alleviation of human suffering.

The state governments are vying with each other to start biotech parks. Despite the hype, none of the parks are as yet functional. Although state biotech parks are a welcome development, there is going to be intense competition more or less for the same targets and some will lose out in this process. While there will be common threads between states in the areas of health and agriculture, each state has also to do some exercise on its unique environment and capabilities. It is also not a bad idea for a few states to get together and be benefited based on their mutual strengths. Caution has to be exercised to see that biotech parks do not become prime land for property developers.

Finally, there is this question of whether we are spreading our resources thin by attempting to get into all areas. There is always a school of thought that we should concentrate on a few and come out as winners. But, I personally feel that biotechnology by virtue of its enormous spread from global business to social concerns, does not really lend itself to choose a priority. We need to work on different fronts and in fact, many biotech products can be developed by small entrepreneurs who need to be encouraged in thousands. This may be more profitable than expecting blockbusters from big corporations. The bottom line is: India missed the industrial revolution and is still paying for it. It cannot afford to miss the biotech revolution.

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Food plants and feeding habits of Himalayan ungulates

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A review of information available on the food plants and feeding habits of Himalayan ungulates revealed that of the 12 alpine ungulate species only four have been studied in detail. Analyses of the compiled data on food plants show that a total of 140 wild plant species are palatable to different ungulate species. However, information on palatability of many other plant species is lacking. The information on the food plants of domestic ungulates is also scarce. Based on whatever information is available it was found that out of 140 plant species, 13 are common in the diet of wild and domestic ungulates. Some of the recent studies have given some indications of a competition existing between wild and domestic Himalayan ungulates for food, hence it becomes imperative to study their feeding habits and document their food plants.

The Himalayan region sustains a diverse array of wild and domestic ungulates[1], besides a large number of small herbivores[2]. A perusal of the literature on the food and food habits of Himalayan ungulates reveals that out of the total 12 wild ungulate species inhabiting the sub-alpine and alpine zones of Himalaya, only four have been studied. Majority of the work on feeding ecology of ungulates is restricted to temperate and sub-alpine regions, while a few studies have been done in the trans-Himalaya. Besides direct observations, faecal pellet analysis that was initiated in the western countries in the early 20th century, has been widely used to assess the feed composition of ungulates. It involves the microhistological analyses of dung and its comparison with the reference slides of food plants available in the study area. Though it has a limitation of differential digestion, it is one of the best methods to document the diet of wild animals. Initially Schaller[3] reported the feeding patterns of different mountain ungulates but did not provide their detailed dietary profile. It has been found that different ungulate species have varying food and feeding habits. Some are purely grazers such as kiang and Himalayan tahr, others such as serow mostly browse while species such as musk deer are mixed feeders (graze and browse). Later, Green[4], Mishra and Johnsingh[5] and Ilyas[6] studied the diet of temperate and sub-alpine ungulates. Green[4] found that the Himalayan musk deer (*Moschus chrysogaster*) avoided graminoids and thrived on poorer quality diets such as lichens and mosses during winters. Brown oak (*Quercus semecarpifolia*) and *Gaultheria nummularia* (tinglu) also formed important diet components during winter when most of the forbs were under snow. Mishra and Johnsingh[5], on the other hand, found that the proportion of graminoids was high in the diet of goral (*Nemorhaedus goral*) for all seasons (92.2% in winters and 98.3% in summers). Similar results were obtained by Ilyas[6]. However, information on the diet composition and food plants of most of the Himalayan ungulates such as tahr (*Hemitragus jemlahicus*), Tibetan argali (*Ovis ammon*), shapu (*Ovis orientalis*) and kiang (*Equus hemionus kiang*) is virtually lacking. Recently, Manjrekar[7] conducted a detailed study on the feeding ecology of Himalayan ibex (*Capra ibex sibirica*) in the trans-Himalaya region. Food habits of bharal (*Pseudois nayaur*) and domestic livestock formed a part of another study carried out by Mishra[8] in the trans-Himalayan region. Both the studies revealed seasonal food selectivity by these animals. Manjrekar[7] found that ibex had highest food selectivity in spring (Preference index = 10.79) and least in winters (Preference index = 0.98). Fruits of wild rose (*Rosa webbiana*) accounted for *ca*. 24% of the diet of ibex in winters. Mishra[8] found that all the ungulate species had a diverse diet in summer compared to winter, when resources become even scarcer. Both the studies have emphasized on the need for studies on the dietary overlap between different ungulate species. Though some of the food habit studies have been carried out on the mountain ungulates of Nepal and Tibet[9–11], information on this aspect is lacking from the alpine ranges of Indian Himalaya.

Perusal and analyses of the pooled data on the botanical composition of diet (Table 1) shows that a total of 140 wild plant species are palatable to different ungulate species, which constitutes *ca.* 9% of the alpine flora of the Western Himalaya[12]. It was also revealed that of the total 44 families of documented food plants, most of the highly consumed food plants belonged to families Rosaceae and Asteraceae (14 each), followed by Fabaceae (13) and Polygonaceae (10).