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MEDICAL BIOTECHNOLOGY: THE INDIAN SCENARIO

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Introduction

Medicines are indeed a boon for the suffering living being, be it an animal or a human being. From time immemorial man has been on the lookout for medicines to relieve pain and suffering. The field of Biotechnology has provided solutions to many health care problems. If at all Biotechnology has revolutionized any sector, we could tell without doubt that it is the medical field. Indian Biotech companies are not far behind in contributing to the world of medicine. In fact, the Bangalore based company, BIOCON is listed one among the top 10 Biotech companies of the world.

History of Medicines

The Ancient Greeks, Romans, Egyptians and Indians had a great deal of knowledge on medicines and the medical knowledge that they had were evident in the numerous papyruses found in archaeological searches. In the past century, there was a revolution in the field of medicine with the advent of antibiotics. The accidental discovery of Penicillin by Alexander Fleming in 1928 opened new avenues in the treatment of bacterial diseases.[1] 1940s saw the extensive usage of Penicillin and by the end of the Second World

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[1]A. Fleming. "On Antibacterial Action of Culture of *Penicillium*, with Special Reference to their Use in Isolation of *B. influenza," British Journal of Experimental Pathology* 10 (1929) 226–236.

War, Penicillin became widely available and won widespread acceptance. Even before that, in 1910, Ehrlich discovered the first antibiotic drug, Salvarsan, which was used against syphilis.[2]

Tuberculosis had claimed the lives of millions of people in the nineteenth century. In 1943, the first TB drug, Streptomycin, was discovered by Selman Waksman[3] who coined the term 'antibiotics'. Thus antibiotics have been used to treat bacterial infections since the 1940s. Humans felt that they won over bacteria by the introduction of antibiotics. The hopes soon died down with the reports of antibiotic resistant bacteria. Microbes, such as bacteria, viruses, fungi and parasites are living organisms that evolve over time. They mutate at a very fast rate. The drugs used against them would be useless once the microbes become resistant. Tackling the drug resistant bacteria needed a different approach.

There is an array of viruses which cause serious diseases in man. Some of them include AIDS, H1N1, Dengue, etc. Tackling viruses is much more tricky than combating bacteria since many of the viruses make use of human cell machinery to replicate. So, any control measure should be done carefully so as to minimize damage to the host cell. Unlike most antibiotics, antiviral drugs do not destroy their target pathogen. Instead these drugs inhibit the development of viruses. Modern antiviral therapy began in the early 1950s, when methisazone, a derivative of the thiosemicarbazones was found to have activity against vaccinia and variola viruses.[4]

Hurdles in Designing Antiviral Drugs

Designing safe and effective antiviral drugs is difficult, because viruses use the host's cells to replicate. This makes it difficult to find targets for the drug that would interfere with the virus without also harming the host organism's cells. Another headache in finding drugs or vaccines against viruses is because of their sudden and frequent variation by antigenic shift and antigenic drift. An antiviral

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[2]P. Ehrlich and A. Bertheim, "Über das salzsaure *Berichte* der deutschen chemischen Gesellschaft," *Berichte*, 45 (1912) 756.

[3]S.A. Waksman, "Strain Specificity and Production of Antibiotic Substances X Characterization and Classification of Species within the *Streptomyces griseus* Group," *Microbiology*, 45 (1959) 1043-1047.

[4]Bauer D.J., "The Antiviral and Synergistic Actions of Isatin Thiosemicarbazone and Certain Phenoxypyrimidines in Vaccinia Infection in Mice," *British Journal of Experimental Pathology* 36 (1955) 105-114.

drug must have the following important characteristics — it must be able to reach the target organ which the virus is inhabiting, it must be chemically and metabolically stable, it must specifically inhibit virus function without affecting the host functions, it should be readily absorbed and it should not be toxic, carcinogenic, allergenic or mutagenic. Antiviral drugs can be toxic to human cells. The number of viruses that have newly emerged in the last 30 years is more than 30, and these are the ones, responsible for the major disease outbreaks.[5] The emergence of antiviral drugs is the result of a vast amount of knowledge of the genetic and molecular functions of organisms. These details allowed biomedical researchers to understand the structure and function of viruses thereby creating major advances in the techniques for finding new drugs.

Biotechnology aims to target the causes of diseases rather than just the symptoms. And that is why biotechnology offers one of the strongest hopes for patients to treat diseases. Biotechnology offers patients a variety of new solutions such as unique, targeted and personalized therapeutic and diagnostic solutions for particular diseases or illnesses, unlimited amount of potentially safer products, superior therapeutic and diagnostic approaches and higher clinical effectiveness because of the knowledge of the biological basis of the diseases.

Need for Newer Kind of Medicines

Microorganisms including the disease causing pathogenic ones are much smarter than human beings. The moment human beings start thinking that they can exercise full control over the pathogens, they tend to retaliate by getting mutated and becoming resistant to the available drugs. Again the mankind will be in a race to discover newer drugs to control them. Of course they will succeed, but the victory holds good only for a short time, since these microbes change fast and become more and more resistant. Hence there is an ever increasing need for the mankind to be equipped with measures to control these pathogens. Else, they turn deadly and can even eradicate human beings from this planet. It is at this juncture that biotechnology tools become handy. A large number of techniques in this field is employed effectively for diagnostics, preventives and therapeutics in medicine.

[5]http://www.searo.who.int/LinkFiles/Avian_Flu_combating_emerging_diseases.pdf

One of the techniques in genetic engineering, namely, PCR (Polymerase Chain Reaction) is currently employed to diagnose the presence of many pathogens. *Clostridium botulinum* is an anaerobic bacteria which is seen in canned foods and cause a serious disease called Botulism. A very precise method of detecting *Clostridium* in such food samples is by doing a PCR analysis wherein the results are obtained within hours. Another example is the diagnosis of tuberculosis which is difficult to diagnose correctly at the early stages.

The Human Genome Project has substantially contributed to the development of drugs against various diseases. The Human Genome Project which was started in 1990 published its first draft sequence in 2003. The availability of the entire human DNA sequence of more than 20,000 genes, opened up numerous vistas for finding out drug targets in diseased conditions. Pharmacology has gained a lot by this development. In fact this was one of the reasons that many pharmaceutical companies are now developing drugs and diagnostics based on techniques in biotechnology like ELISA (Enzyme Linked Immuno Sorbent Assay), fermentation, site directed mutagenesis, etc.

Clear practical results of the Human Genome Project emerged even before the work was finished. For example, a number of companies, such as Myriad Genetics started offering easy ways to administer genetic tests that can show predisposition to a variety of illnesses, including breast cancer, haemostasis disorders, cystic fibrosis, liver diseases and many others. Also, the aetiologies for cancers, Alzheimer's disease and other areas of clinical interest are likely to benefit from genome information and possibly may lead in the long term to significant advances in their management.[6]

Indian Biotechnology Sector

The Department of Biotechnology (DBT) has helped nurture the biotechnology field in India since its inception in 1986. This sector has grown over the last three decades from the support provided by a host of other organizations such as DST, ICMR, ICAR and CSIR apart from DBT. A large number of companies have also come up in the

[6]N. Naidoo, Y. Pawitan, R. Soong, D.N. Cooper, C.S. Ku, (2011) "Human Genetics and Genomics a Decade after the Release of the Draft Sequence of the Human Genome," *Human Genomics* 5, 6 (2011) 577–622.

private industry which ranges from low turnover companies to biotech giants like Biocon with a turnover of more than 270 million US $.[7] The private industry has grown in strength from a nascent stage in 1980s to a mid-maturity level in 2000s with revenues of US $ 4 billion in 2011.

India with its large talent pool could contribute a lot in this field. With the right support from the Government of India, the combined revenues of the biotechnology and healthcare sectors could reach $100 billion by 2025. The components of this bio-economy will involve all aspects of the biotechnology sector, from new forms of vaccines, novel protein therapeutics, bio-similar manufacturing, improved plant hybrids and renewable energy from biological sources.[8]

Biotechnology has a potential impact on many domains of human welfare, ranging from food security, waste management, health care and environmental protection. Of the different branches of Biotechnology, the single largest contributor to the Indian biotech industry for the past few years is the Biopharmaceuticals which includes vaccines and drugs. The advantages of Indian pharma industry include low R & D costs, large pool of scientists and engineers, institutional infrastructure, diverse patient pool and diverse species of flora and fauna. There are more than 400 Biotechnology companies in India. The top ten Biotechnology companies in India are listed in table 1. Biopharmaceuticals account for 64% of total biotechnology market value.[9]

Table 1 – List of top ten Biotechnology companies in India.[10]

Sl. No:	Name of the company	Headquarters	Year of establishment
1	Serum Institute of India	Pune	1966
2	Panacea Biotech Ltd	New Delhi	1976
3	Biocon Ltd	Bangalore	1978

[7] http://www.biocon.com/docs/biocon_annualreport_2012.pdf

[8] "Indian Biotechnology — The Roadmap to the Next Decade and beyond Report," Life Science World (2012).

[9] http://www.kppub.com/articles/mar2011/the_indian_biotechnology_sector-A_Review.html

[10] (http://top10companiesinindia.com/2013/05/30/top-10-biotechnology-companies-in-india/)

4	Novo Nordisk	Denmark	1923
5	SIRO Clinpharm	Thane	1993
6	Novozymes South Asia	Denmark	1925
7	Shantha Biotech	Hyderabad	1993
8	Indian Immunologicals	Hyderabad	1982
9	GlaxoSmithKline Pharma Ltd.	London	2000
10	Wockhardt Ltd	Mumbai	1960

Medical Biotechnology in India

The contributions of the biotechnology sector to the medical field can be broadly classified into three: diagnostics, preventives and therapeutics.

1. Diagnostics

A prerequisite for proper treatment of any disease is the timely and correct diagnosis. If this is done properly, then the patient could be given the right drug at the right time and his or her life could be saved. The recent outbreaks of viral diseases like HINI, Chikangunya, etc. demanded the need for faster and indigenous diagnostic tools like the ones developed by Rajiv Gandhi Centre for Biotechnology in Thiruvananthapuram. This new multiplex molecular diagnostic kit, based on PCR (polymerase chain reaction), had been developed by HLL in partnership with scientists from the Rajiv Gandhi Centre for Biotechnology.[11]

Development of new kits alone is not enough, but there should be skilled personnel to carry out the tests in an accurate and timely manner. Institutes like NIMHANS played a significant role in waking up to situations which demanded such speedy work by employing skilled personnel for fast and effective diagnosis using modern methods like PCR. The development of indigenous swine flu detection kit was done by three Indian research institutes — Defence Research and Development Organization, Imperial Life Sciences and Ocimum. India has been importing these kits from US (Applied

[11]T.V. Padma, 2007. "New Test Helps Tackle India's Chikungunya Outbreaks," Scidevnet, http://www.scidev.net/global/health/news/protein-change-causes-virus-to-spread.html.

Biosystems) and Switzerland (Roche Diagnostics). These kits are quite expensive and out of reach of common man. But the indigenous kits costs only one third of the imported kits.

2. Preventives

Vaccine development is one of the potential areas in medical biotechnology, which can contribute a lot to better health care. Serum Institute of India, one of the top ten Indian Biotech companies is a leader in the production of vaccines of various categories. This also includes the recombinant vaccines, a few of which are listed in table 2. Serum Institute of India Ltd. has established itself as the world's largest producer of Measles and DTP group of vaccines. It is estimated that two out of every three children immunized in the world is vaccinated by a vaccine manufactured by Serum Institute. Serum Institute of India have recently set up Serum Bio Pharma Park, India's first biotech Special Economic Zone (SEZ). Recently the Biotech giant Biocon launched ALZUMAb™, world's first novel anti-CD6 antibody to address a large unmet need for the treatment of Psoriasis in India.[12]

Biocon has also entered into an agreement with Mylan for the global development and commercialization of Biocon's generic insulin analog products (long lasting insulins), which has a global addressable market of US$ 11.5 billion. Shanvac B is a popular recombinant Hepatitis B vaccine launched by the Hyderabad based Shantha Biotech. Bharat Biotech launched the world's first clinically proven conjugate Typhoid vaccine 'Typbar-TCV', which offers long-term protection and can be given to children as young as six months.[13]

Table 2: List of recombinant vaccines produced by Serum Institute of India.[14]

Brand name	Vaccine use
Gene Vac-B	Recombinant Hepatitis-B Vaccine
SII Q-Vac (Quadrivalent Vaccine)	Diphtheria, Tetanus, Pertussis & Hepatitis-B Vaccine (Adsorbed)
Pentavac	Diphtheria, Tetanus, Pertussis (Whole Cell),

[12]http://www.biocon.com/biocon_products_bio_BF_alzumab.asp
[13]http://www.ibef.org/industry/biotechnology-india.aspx
[14]Source -http://www.seruminstitute.com/content/products/product_list.html

(Lyophilized)	Hepatitis B (rDNA) & Haemophilus Type b Conjugate Vaccine (Adsorbed)
Quadrovax (Lyophilized)	Diphtheria, Tetanus, Pertussis (Whole Cell) and Haemophilus Type b Conjugate Vaccine (Adsorbed)

Rotavirus is responsible for approximately 4.5 lakh child deaths due to diarrhoea globally each year. It is particularly threatening in India where around 1,00,000 children die each year from severe diarrhoea and dehydration caused by rotavirus. India accounts for 22 per cent of the estimated global deaths from diarrhea causing rotavirus. An Indian-made rotavirus vaccine, Rotavac, was developed and announced in 2013 by Bharath Biotech. The cost of this indigenous vaccine is estimated to be only one by twentieth of the currently available foreign ones.[15]

3. Therapeutics

Biotechnology has solutions to cater to the requirements of the therapeutic side too. The term "advanced therapies" comprises three new techniques that are revolutionizing modern medicine: cell therapy, gene therapy and tissue engineering. Tissue and organ engineering indeed has a lot of applications in the field of medicine.

Stempeutics is the first Indian company to get approval from DCGI (Drugs Controller General of India [may be called an Indian equivalent of FDA]) for conducting stem cell clinical trials in India in 2009. Stempeutics has done pioneering work in the isolation, up-scaling and large scale production of adult mesenchymal stem cells for therapeutic applications. Currently three Phase 2 clinical trials are in progress in India which are approved by DCGI — Critical Limb Ischemia, Osteoarthritis and Liver Cirrhosis. Stempeutics expects to launch its first "stempeucel®" cell therapy product for the treatment of Osteoarthritis/Critical Limb Ischemia (OA/CLI) in the market by 2015.[16]

Stempeutics has collaborated with Cipla for marketing its products in the near future. Under this alliance, Cipla is sponsoring upto Rupees 50 crores (1 crore=10million) in Stempeutics in the initial phase for research and development of stem cell based products. This

[15] www.thehindu.com/sci-tech/...rotavirus-vaccine/article4714757.ece
[16] http://www.stempeutics.com/stempeucel.html

is a classic example wherein a marketing company invests a lot of capital in the R & D sector of a manufacturing company. The Government of India has many priorities other than R & D in the field of Science, since it is only a developing nation. In such a scenario, public–private partnership will go a great deal in getting fruitful results in drug discovery.

Recently the Bangalore based Biotech company BIOCON has launched ALZUMAb, a biologic drug for the treatment of auto-immune disease psoriasis. This is the second biologic drug from BIOCON, the first one being BioMAb-EGFR developed in 2006 to treat head and neck cancer. ALZUMAb is the world's first novel anti-CD6 antibody to treat psoriasis. Its cost is only 50% of the currently available drugs used for Psoriasis treatment. Also, the remission period of ALZUMAb was estimated to be around 28 weeks whereas for the other drugs for Psoriasis it was 5-20 weeks. Biocon is also credited with the discovery of the world's first Pichia-based recombinant human Insulin, INSUGEN. Biocon Limited has been ranked No. 6 on the annual Global 'Top Twenty Employers' list for the Bio-Pharma sector by science magazine in 2013. This is a significant jump from No. 19 in 2012. Biocon is the only Asian Company to be a part of the Top 20 Elite List which includes leading global innovator companies.[17]

Bioinformatics can play a significant role in candidate drug development. Computer aided drug design involves determination of the three dimensional structure of the viral molecules using X-ray crystallography. This is followed by computer simulation and thermodynamic computation to study the atomic interaction with other molecules in order to screen out the structure with favourable binding characteristics.[18]

Nanomedicine

Prof C.N.R. Rao, Chairman, Science Advisory Council to the Prime Minister of India said in 2006: "We missed the semiconductor revolution in the early 1950s. We had just gained independence. But with nanoscience and technology, we can be on an equal footing with the rest of the world."[19] Nanomedicine, a branch of nanotechnology

[17]http://www.biocon.com/docs/Biocon_Science_Top20_Employers_25Oct2013.pdf

[18]B. Bean, (1992) "Antiviral Therapy: Current Concepts and Practices," *Clinical Microbiology Reviews* 5, 2 (1992) 146-182.

[19]http://www.academia.edu/2276198/Nanotechnology_Development_in_India_Investigating_Ten_Years_of_Indias_Efforts_in_Capacity_Building

involves diagnosing, treating, and preventing disease and traumatic injury, of relieving pain, and of preserving and improving human health, using nanoscale structured materials and biotechnology. The scientists in the field of regenerative medicine and tissue engineering are continually looking for new ways to apply the principles of cell transplantation, material science, and bioengineering to construct biological substitutes that will restore and maintain normal function in diseased and injured tissue. Development of more refined means of delivering medications at therapeutic levels to specific sites is an important clinical issue, for applications of such technology in medicine, and dentistry.[20]

Nanotechnology allows encapsulation of potent drugs in tiny particles measuring miillionths of a millimetre in diameter. This superior and novel technology is opening up new options for therapeutics — in super-accurate drug delivery, in increasing precision hits at the site of disease and in having fewer side effects. Nanotechnology has significant roles in supplying nanomaterials for creating such artificial skin and other tissues. Various kinds of scaffolds are required for creating such tissues and organs artificially.

The two most common forms of 3D cell culture systems are the prefabricated scaffold and the hydrogel. Scaffolds can be made from natural or synthetic materials and, through the use of various production techniques, can be engineered with diverse pore and fibre sizes to allow cells to migrate and grow within the network of the scaffold.[21] A hydrogel is a biologically compatible (biocompatible) polymer network with high water content and physical properties that closely mimic the natural extracellular matrix (ECM). Like the prefabricated scaffold, hydrogels can be made of either natural or synthetic materials and can be produced with various pore sizes.[22] Cancer cells can be cultured either in or on a hydrogel.

Nanotechnology provides an array of options (for example polylactic acid) as scaffold materials. However, biomaterials are frequently used to fabricate 3D scaffolds. Scientists in the Material Science division of Indian Institute of Science are doing a

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[20]"Forward Look Report on European Nanomedicine," European Science Foundation, 2005.

[21]D. Liang, B.S. Hsiao, B. Chu, "Functional Electrospun Nanofibrous Scaffolds for Biomedical Applications," *Advanced Drug Delivery Reviews* 59 (2007) 1392-1412.

[22]A.C. Jen, M.C. Wake, A.G. Mikos, "Hydrogels for Cell Immobilization," *Biotechnology and Bioengineering* 50 (1996) 357-364.

commendable work in developing various scaffolds for tissue engineering. Cells exist inside the body, that is, under *in vivo* conditions in a 3D environment. Therefore cells cultured in a 3D environment *in vitro* using biomaterial scaffolds are more likely to behave better physiologically than those cultured on a 2D surface.[23]

Indian Biotechnology Regulatory authority

The regulatory bodies in the field of biotechnology in India include Recombinant DNA Advisory Committee (RDAC), Institutional Bio-safety Committee (IBSC), Review Committee on Genetic Manipulation (RCGM), State Biotechnology Coordination Committee (SBCC) and Recombinant Drug Advisory Committee (RDAC).

The Central Drug Standards Control Organization (CDSCO) regulates drugs, cosmetics, diagnostics and devices in India. The CDSCO is headed by the Drug Controller General of India (DCGI). This is equivalent to US FDA. The CDSCO is responsible for the safety, efficacy, and quality standards for pharmaceuticals and medical devices, and publishes the Indian Pharmacopoeia. The DCGI is advised by the Drug Technical Advisory Board (DTAB) and the Drug Consultative Commission (DCC). All licenses for medical devices are handled by the Central Licensing Approval Authority (CLAA).

Conclusion

Indian Biotechnology is poised for a substantial growth. Countries like Singapore, China, etc. are fast developing their technologies in the field of nanomedicine and stem cell therapy. India has a number of good research institutes like the Indian Institute of Science, Indian Institute of Technologies (IITs), AIIMS, JNCASR, NCBS, etc. All these research institutes are already doing many projects in these upcoming fields of medicine with the funding from agencies like DBT, DST and ICMR. With the right kind of policies from the side of the Government of India including the regulations and export policies and with an increasing number of public private partnerships, India can contribute tremendously to this field. This is all the more the need of the hour, since mankind has to deal with a multitude of diseases thanks to the lifestyles we all practice these days.

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[23]C.G. Simon, Y. Yang, S.M. Dorsey, M. Ramalingam, K. Chatterjee, "3D Polymer Scaffolds," *Methods in Molecular Biology* 671 (2011) 161-174.