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ACKNOWLEDGEMENT. I thank the Reserve Bank of India for funding my Fellow Programme in Rural Management at the Institute of Rural Management, Anand.

Satyendra Nath Mishra is in the Institute of Rural Management, Anand 388 001, India. e-mail: saty.nm@gmail.com

The biotechnology pyramid: basic science to application of science

Seshagiri Raghukumar

Biotechnology is the buzzword in biology, and not without reason. The apparently endless opportunities that biotechnology offers in terms of new products, processes, improved health and comfort[1], as well as job opportunities, are drawing present-day research students, who consider this to be the most important topic of biology. This leads to debates about what research topic would be important and what would not, which Ph D topics are to be selected and which are to be discarded and which laboratories and research supervisors are to be sought after and which are not. There often seems to be some confusion about what actually leads to good biotechnology research, an issue not only with research students but with senior scientists as well. Biotechnology is an important branch of science that aims to benefit human society. However, I would like to argue that high standards in biotechnology research can be achieved by asking 'what is interesting', as much as 'what is important'. While one does not doubt that science has to ultimately resolve societal problems, such ends are not achieved only by focusing on societally relevant issues, thus leading to a catch-22 situation. How does biotechnology work then?

Basic sciences to application: the biotechnology pyramid

Technology rests on a base of science, small or large. A technology emerges when the science is put to use as a product or process for the benefit of the human society, in the form of medicine, food, beverages, chemicals, textiles and others. Technology development is the end result of a process that science undergoes. I will illustrate this with a few of my favourite examples.

The green fluorescent protein (GFP) as well as other fluorescent proteins are now important molecular biology tools, being used as reporter genes in gene expression studies[2,3]. The GFP gene fused to the gene of interest lights up the cells under an epifluorescence microscope when the gene under study is expressed, thus providing important information to the researcher. The story of GFP started in the 1960s with the research interest of Osamu Shimomura on the fluorescence of the jellyfish *Aequorea aequorea*. He spent the next 20 years in basic research that led first to identifying GFP as being responsible for the fluorescence, subsequently purifying it, crystallizing it and characterizing the protein. Then Martin Chalfie successfully cloned and expressed the GFP gene in *Escherichia coli*. In the mid 1990s, Roger Tsien was responsible for developing this technology further for gene expression studies and was deservedly awarded a Nobel Prize in Chemistry in 2008. Tsien's achievement was based solidly on his own enormous expertise in the chemistry of GFP and also the foundation of GFP science that had been laid by then by a few key scientists. Understandably, therefore, Tsien was not the only recipient of the Nobel Prize. Martin Chalfie was the second recipient of the same Prize. It would be easy to state that these two were the biotechnologists who were responsible for the fluorescent protein technology. However, it is not quite so. The entire edifice of GFPs, prior to the work of Chalfie, Tsien and a number of other students and researchers, rested on the science that was built up by Shimomura, who became the third recipient of the Nobel Prize. In the words of Marc Zimmer[4], 'I hope that

this award will remind those in charge of funding research that basic research can open the doors to very useful and often unexpected discoveries. On the other hand I hope that the award will also silence the purists who do not value applied research.' Presently, a number of companies market an array of fluorescent proteins with different optical properties in the form of recombinant DNA plasmic vectors for various molecular biology applications.

The omega-3 polyunsaturated fatty acid (ω-3 PUFA), docosahexaenoic acid (DHA), is an important compound for cardiovascular health in humans[5] and for reproduction in aquaculture fish and crustaceans, including prawns[6]. While fish oil had been the standard source of DHA earlier, a microbial source derived from the marine, heterotrophic microalga *Schizochytrium* (*Aurantiochyrium*) *limacinum* is now gaining a greater share of the market. Between 1971 and 1986, the importance of DHA in human health had been studied widely and its use had become accepted. However, the story of this major microbial nutritional product began more than 40 years ago in a manner totally unrelated to the health effects of this polyunsaturated fatty acid, when Ellenbogen *et al.*[7] published a paper on the fatty acid composition of the marine stramenopilan 'fungi' or microalgae, the thraustochytrids. They discovered that DHA was a signature fatty acid of these microalgae. Their intention was to use fatty acids as a taxonomic index, a parameter that had begun to become popular in bacterial taxonomy[8]. Later Findlay *et al.*[9] studied in detail how DHA could be used to study ecological dynamics of these microalgae in decaying mangrove leaves. Using this base of information, William Barclay (Omega Tech, USA) developed the process to produce microalgal DHA in the early 1990s after several years of screening and optimizing culture conditions. Barclay and his group at Omega Tech and later at Martek Biosciences refined the technology of microbial omega-3 oil to a high level of competitiveness in the market[10]. Their process achieves more than 100 g of dry weight biomass containing at least 50% of PUFA-rich oil with a very high DHA content. In a way, it is right to say that Barclay was the pioneer of this technology. His genius lay in tying together all previously available information and venture daringly with a conviction that thraustochytrids could be commercially used to produce DHA for aquaculture purposes in the initial years, and for human health later on. DSM, a major health, nutrition and materials company from The Netherlands is the single largest manufacturer of this microalgal DHA, which it acquired partly from Martek Biosciences, which had earlier acquired Omega Tech. A variety of health foods and beverages are now available containing DSM's microalgal DHA.

Imatineb, sold as Gleevec or Glivec by Novartis is a drug to treat multiple cancers, particularly chronic myelogenous leukaemia (CML)[11]. The story has its beginning in the discovery of Janet Rowley in 1973 that the abnormal 'Philadelphia chromosome', discovered consistently in patients with CML by Peter Nowell and David Hungerford in the 1950s, was actually the result of a translocation between the long arms of chromosomes 9 and 22. More than ten years later, it was discovered that the translocation contained a fusion between the break-away cluster region (*bcr*) on chromosome 22 and the oncogene *abl* from chromosome 9. They concluded that this *bcr–abl* fusion was responsible for CML. The actual function of the *bcr–abl* fusion itself was not resolved till 1990, when Lugo and others from the University of California, LA, discovered that the fusion resulted in an abnormal tyrosine kinase protein that is not properly regulated. Once the mechanism was known, it was a matter of time before a compound that targeted the *bcr–abl* fusion was discovered. By 1998, Brian Druker (Oregon Health and Science University) had collaborated with Novartis (then Ciba-Geigy) to discover that the synthetic compound they called ST1571, presently the drug Gleevec, inhibited the functioning of the *bcr–abl* fusion. The drug has been in use since 2001 to treat CML. In the words of Pray[11], 'the Gleevec story is no less an excellent, and some would say, beautiful example of how knowledge of the biological functioning of a cell can lead to life-saving medical treatment'.

How is biotechnology achieved?

A few points become clear when one traces the origin of the above three, as well as of many other biotechnologies.

First, an innovator is required at the end of the chain – who has the genius to bridge the gap between science and its application, thus justifying Louis Pasteur, who said that there was no such things as pure and applied science; there was only science and the application of science.

Secondly, it is important to recognize that the innovator stands in the position of Isaac Newton, who was reputed to have said 'If I have seen further it is by standing on the shoulders of giants'. This implies that the second prerequisite is that of the giants who contributed to the building of the science that preceded the application. Hence, the role of scientists who contribute to the building of the base itself cannot be ignored. More often than not, such scientists who contributed to a technology would have had no clue that their study would lead to an application some day. All those who contributed to the base of biotechnology were people who sought answers for an interesting question in biology. Shimomura had no idea at all about the application of the GFP when he started the work. He was only addressing his curiosity about the cause of fluorescence in jellyfish and subsequently the nature of the protein. Nor did Chalfie have any specific technology in mind when he cloned the GFP gene. The only reason that Ellenbogen *et al.* studied the fatty acid profiles in thraustochytrids was because of the inherent taxonomic use of the same. Findlay was interested in ecological dynamics. Understanding the mechanism of *bcr–abl* fusion was the primary aim for Lugo and others while addressing CML. However, all these researchers were ultimately responsible for the final technological product by building a base for the technology. Technology, thus, is team work.

Thirdly, it is important to recognize that a technology takes several years to build. It is a fallacy to think that a technology can be built overnight. In order to build up a sufficient amount of scientific base or edifice that is built on the skills and expertise of a number of scientists is time-consuming.

The biotechnology industry and the academia

The biotechnology industry is driven by economics. It seeks highly innovative applications that are novel, useful and economical and which can be most competitively marketed. A knowledge of the

market, therefore, is inherent to development of the biotechnology application.

Knowledge of the market scenario is the forte of successful industries, who then seek out academics to accomplish their goals. What then do such industries require from academic scientists?

In one case, demand for a marketable product may exceed supply, allowing many other players to enter the market. In such a case, an industry requiring an academic partner will seek one who has technical expertise in that particular field.

In the second case, the market for a product may have attained saturation and a new entrant will need an improved process to compete in the market. A good example is the work of the CSIR Institute of Microbial Technology (IMTECH), Chandigarh, whose expertise helped in developing a clot-busting drug so important in treating myocardial infarctions – streptokinase, an important drug for dissolving blood clots. The drug was available in India till about 15 years ago only as an expensive one that was based on rDNA processes to produce tissue plasminogen activator. Expertise of IMTECH scientists, under the leadership of Girish Sahni, helped to develop a cost-effective process using streptokinase produced by a strain of the bacterium *Streptococcus*, after several years of study. The technology was sold to Cadila Pharma Ltd. This helped in indigenizing its manufacture, cutting down the cost of this important drug and helping Cadila market it in a highly competitive manner. Sahni's team has further improved the process by developing a recombinant streptokinase from *E. coli* and transferred the technology to Shasun Drugs and Chemicals, Chennai[12]. Yet again, the demand might exist but not the supply. Examples are the lack of drugs for many diseases and lack of economical processes for biofuel. Very often, the technologies themselves might not have been envisaged as with the case of the GFP technology discussed earlier. These situations call for innovation and industries seek academic partners who could help. It is not easily predictable as to who these academics are, since the term 'innovative' itself indicates that the solution is 'out of the box'. It also means that the solution may come from any area or field of research. The usual sources of innovation in modern times are from basic research in genomics, proteomics, transcriptomics, oncology, immunology and other modern branches of biology. Often many traditional specializations, such as expertise in special groups of organisms, or even old-fashioned, esoteric branches of science could be useful. 'Translational research', which aims to develop basic research discoveries into improvement in technologies helps reduce the time lag between basic sciences and their application to develop a technology, and has been much encouraged in recent times[13]. This truly represents the spirit expounded by Pasteur with regard to application of sciences.

What kind of research should academics involved in biotechnology carry out then? As mentioned before, knowledge of the market is inherent to development of the biotechnology application. One may find a market-savvy academic, who is also equipped with imagination to put his science to use. However, by and large, academics may not be fully aware of market demands. As a matter of fact, they are not required to. It is not ignorance of the market that hampers good academic research in biotechnology, but the pretension that one knows the market and is developing technologies for industries. This ignorance leads to repetitive, unimaginative research topics akin to reinventing the wheel, such as routine screening for well-known applications with already saturated markets. Ph D students are often led to believe that they are working on important areas of biotechnology. We often hear researchers mention how 'important their work is' while presenting their study. One focus of research in biology and biotechnology should be around the question of what is important. However, based on the examples I have cited above, I would like to suggest that breakthroughs in biotechnology arise equally by pursuing questions that are fascinating, but not necessarily what is important. It will be good to hear at least a few budding researchers mention in their presentation how they chose a topic because a particularly interesting scientific puzzle fascinated them. One would further like to hear them say a few years later how they diligently pursued their fascination and how that idea became part of a technology through their own efforts, or even someone else's. The future of innovative biotechnology lies in a balance between importance and fascination.

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Seshagiri Raghukumar is in Myko Tech Private Limited, 313 Vainguinnim Valley, Dona Paula, Goa 403 004, India.
e-mail: s_raghukumar@mykotech.com