ESSAY

BIOTECHNOLOGY: MARKETS AND BIOETHICS

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Biotechnology consists on the utilization of living organisms or its components for the production of goods and services. For the most part, biotechnological processes are considered to be more efficient and environmentally friendly than those based on traditional technologies. The present article argues in support of the following contentions: 1) Due to its technical simplicity and to the presence of strategic niches of localized interest, BT represents an appealing option for developing nations; 2) Sound knowledge instead of ideology or myth must be the criterion driving the adoption of applications that may elicit some controversy, such as the production of biofuels or the cultivation of genetically modified crops, and 3) The respect for human dignity must be the foremost principle to have in mind in the design of novel therapies involving manipulation of human embryos.

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The rise of modern biotechnology

The 20th century witnessed revolutionary advances in the sciences. In the early decades, the physical sciences underwent a conceptual reformation with Einstein's theory of relativity and Max Plank's quantum mechanics. By mid century, it would be the turn of biology, with Watson and Crick's unraveling of the structure of DNA. Somewhat later, during the 70s, biology would undergo another explosive impulse with the development of modern biotechnology (BT), made possible due to the discoveries in molecular biology.

Since scientists, entrepreneurs and public policy makers usually assign different meanings to BT, for the purpose of this presentation BT will be defined as the utilization of living organisms or its components for the production of goods and services. This wide definition tells us that BT has been employed for centuries. Fermentations in the food & beverage industry and the microbial production of antibiotics by the pharmaceutical companies are typical examples of traditional BT. Modern BT, instead, may involve the transferring of genes among species in the laboratory, a technique dubbed genetic engineering. The genes can be expressed in the recipient organism because the genetic code is universal. Modern BT may also encompass the manipulation of embryos and cells, or the utilization of advanced software for further developments in genomics, proteomics and metabolomics.

The textbook example of genetic engineering is the production of insulin. Before the advent of modern BT, diabetics used a hormone isolated from bovines or sheep. Nowadays, these patients consume genetically engineered human insulin produced by microorganisms, which is both cheaper and more pure than the insulin isolated from animals. The world market of this so called recombinant insulin approaches US$ 3.0 billion per year. Another interesting application of genetic engineering is the production of vaccines. Traditional vaccines against viral infections consisted of viral preparations that had been inactivated by some procedure that harmed their genetic material. Occasionally, these vaccines induced the very disease they were supposed to prevent, as the viral inactivation was not completely effective. Since the immune response is triggered by the proteins associated to the viral genome, the genes encoding these proteins can be cloned in various cells for their production in large quantities. Several vaccines presently available in the market consist in recombinant proteins obtained by genetic engineering, which in addition to reducing production costs, are safer than inactivated virus. A typical example is the vaccine against hepatitis, which has a world market of US$ 1.4 billion per year.

Horizontal gene transfer has also been applied with plants. In spite of being a highly controversial issue (see below), the global area of genetically modified crops shows a steady increase of about 10% every year. The main transgenic crops are soybean (57%), maize (25%), cotton (13%) and canola (5%). Other important transgenic crops are rice, squash, papaya and alfalfa. The preferred traits transferred to these crops are herbicide tolerance (68%) and insect resistance (19%)[1].

Gene transfer to oocytes that have recently been fertilized *in vitro* allows transgenesis in animals. To date, the main application foreseen in this field is the production of human proteins of therapeutic value. The genetic modification is designed in such a way that the transgenic animal produces large quantities of a valuable protein in one of its fluids, typically milk. To date, the only authorized product is human antithrombin III produced by goats, although alpha-antitrypsin and lactoferrin produced by sheep and rabbits, respectively, are at an advanced stage of testing.

As mentioned before, cell manipulation was another key technique that boosted modern BT. *In vitro* plant tissue culture allows the cloning of plants for agriculture, forestry or horticulture interest. In the case of animal cells, fusion of a lymphocyte with a cancer cell makes a hybridome, an immortal cell that produces highly specific (monoclonal) antibodies, widely used by the pharmaceutical industry and in basic research. The production of stem cells from early-stage mammalian embryos (blastocysts) constitutes another paradigmatic example of cell manipulation. These cells are capable of unlimited growth in culture and possess the ability to differentiate into virtually any tissue of the body. Therefore, they are thought to be a source of regenerative tissue for deteriorating organs. Fragmenting human embryos to derive pluripotent stem cells has deep ethical connotations, which will analyzed later in this article.

One of the distinctive features of modern BT is the short time elapsing between a scientific finding and its practical applications. Today, there are about 4,300 companies that base their production processes in gene or cell manipulation using animals, plants or microorganisms. Of them, nearly 1,900 are in North America, 1,600 are European and 750 are located in Asia. There are some successful companies in Latin America as well, particularly in Brazil, Argentina and Chile. The revenues reported in 2006 for these companies were US$ 73.5 billions, whereas their R&D expenses approached US$ 28 billions[2]. Approximately 10% of these modern BT based companies, which do not

[1] Data obtained from www.isaaa.org.

[2] Lawrence, S.: “State of the biotech sector, 2006.”. *Nature Biotechnol* 25, 706, 2007.

include pharmaceutical companies, medical device companies or contract research organizations, are publicly traded on stock exchange. However, business has not been easy for these companies, as demonstrated by the frequent partnerships, mergers and acquisition deals that take place in this sector.

In spite of the notable innovations introduced by modern BT, the benefits of traditional BT should not be underestimated. Processes such as the production of alcoholic beverages, fermentations in the dairy industry, anaerobic digestion of waste, biological treatment of domestic and industrial wastewater, bioremediation of soils, production of antibiotics, etc., continue to play a major role in the BT industry even though, for the most part, they utilize microorganisms that have not been subjected to genetic engineering.

Traditional BT is also thriving in the field of enzymes. These catalytic proteins have numerous industrial applications (food and beverage, detergents, animal feed, diagnostics, forensics, bioethanol, cellulose, leather, textiles, etc.), as well as in research. The present world market sitting slightly above US$ 4 billion is expected to escalate to nearly US$ 5 billion by 2009[3]. Traditionally, developed nations have concentrated most of the demand due to the high value-added nature of the product. More recently, however, countries such as China, Taiwan and India have emerged as global manufacturer centers, thus contributing to the growing trend of the market.

BT is an appealing option for developing nations

Some might think that BT, either traditional or modern, requires highly skilled personnel and large investments, and therefore it would be suited only for industrialized nations. In fact, the great majority of companies based on modern BT, as well as the large pharmaceutical and food companies, have their headquarters in these countries. However, BT offers a unique opportunity for generation of wealth and social progress in developing nations. This contention is based on two arguments. First of all, the technologies involved in cell and gene manipulation are actually unsophisticated and of low cost. They can therefore be easily adopted by research institutions and industry in most countries of the globe. Secondly, it is possible to find strategic niches that are of localized interest. Experiences in this sense are the world leadership of Brazil in the production of bioethanol, the efforts of academia and industry in South Africa to combat AIDS; the

[3] http://www.the-infoshop.com/study/fd31270-enzymes.html.

development of a vaccine against SARS in China and the production of the first vaccine against meningitis B by the Cubans.

Chile can also demonstrate some efforts in this respect. An interesting example is the production of a vaccine for salmons. Chile is the second producer of farmed salmon in the world, with exports approaching US$ 1,700 per year (~3% of Chilean exports). It is estimated that the present annual production of 600.000 tons will double in the next five years. However, every year salmon farmers are loosing about US$ 200 million due to a deadly disease called salmonoid rickettsial septicemia (SRS), which is caused by the bacterium *Piscirickettsia salmonis*. Since this microorganism induces an intracellular infection in the fish, standard vaccines based on attenuated or dead bacteria do not exceed 30% efficiency. A group of partners from private companies and foundations decided to engage in the development of a highly efficient vaccine (at least 70% effective) that at the same time would be of low cost. Since the overall selling price per salmon is less than US$ 10, it was estimated that each treatment could not cost more than US 10 cents. The partners participating in this project were the private Foundation Science for Life, the company BiosChile, the Canadian company Acqua Health Ltd, Novartis Animal Health and Fundación Chile, which is a joint venture between the Chilean government, ITT Corporation and BHP Billiton.

The development of the SRS vaccine was undertaken in several stages. First, the genome of *P. salmonis* was sequenced and through comparative genomics with other bacteria, 16 genes were selected for antigen production. These antigens were produced by means of recombinant DNA techniques in the bacterium *Escherichia coli* and thereafter tested in various combinations in *P. salmonis* infected fish. An immunity response of 90% efficiency was obtained with a crude extract containing a mixture of three antigens. Large scale production of the vaccine formally started in 2006 in the Novartis industrial facilities in New England and in Canada, and commercialization was already taking place by the end of that year. Since *P. salmonis* proliferates only in the Southern hemisphere, the market to date for this vaccine has been principally Chile. However, fish farmers in the Northern Hemisphere do not rule out the possibility that the bacterium may appear there, as they are constantly checking for its presence using a kit produced by BiosChile. On the other hand, Novartis has decided to increase the added value of this product by including antigens for other fish diseases. Thus, in addition to the SRS vaccine already described, two multivalent vaccines are also being produced: one that immunizes against SRS, infectious pancreatic necrosis virus and *Vibrio ordalii*, and another that immunizes against SRS and *Aeromonas*. The whole project including the initial research, the

developmental phases and full-scale production took about seven years, with a cost of approximately US$ 5 million. In a scenario where no effective vaccine currently exists, this product is expected to achieve a US$ 30 million market, allowing savings of US$ 130 million to the Chilean salmon industry.

This case clearly illustrates how collaboration and appropriate alliances can lead to innovation in a country with a relatively limited technological background. None of the individual actors in this project had the necessary skills and knowledge to solve the problem individually. But thanks to BiosChile genomic competences, Foundation Science for Life's scientific experience, Fundación Chile's know-how and fish testing facilities, and Novartis' production and commercialization capabilities, these partners developed and commercialized a successful vaccine. Based on the success and experience gained in this project, this collaboration is now conducting research on the bacterium *Streptococcus focae*, which also affects the Chilean salmon fish population.

Another interesting Chilean effort is copper bioleaching, an application that is being optimized through scientific research for better profitability. The mining companies presently obtain this metal either by pirometallurgy or hydrometallurgy. The first process, employed mainly with ores enriched in copper sulfides, involves crushing and screening of the metal ore, flotation of the fine sulfides, smelting to form blister copper (97%-99%) and refining by electrolysis or by heat. In turn, hydrometallurgy is intended for ores enriched in copper oxides. In this case, the crushed ore is deposited on a heap possessing a series of hoses dispensing dilute sulfuric acid. The leached solution containing dissolved copper is subjected to solvent extraction with a chemical substance that binds to and selectively extracts the metal. This substance is later stripped from the copper for reuse; the concentrated copper suspension is dissolved in sulfuric acid and sent to electrolytic cells for recovery of copper cathodes. Either of these processes leaves behind a significant fraction of the copper originally present in the ore. Therefore, a procedure to recover this residual copper or to extract copper from low grade ores that are not exploited for economic reasons would be of great value to the mining industry.

BT offers a solution to this problem. There are bacteria that obtain the energy required for reproduction and growth by oxidizing copper sulfides. These bacteria are normal inhabitants of copper mines and when they are present in irrigated dumps or heaps, the leaching of copper with dilute acid becomes more efficient. Bioleaching of sulfide rich ores takes longer than chemical leaching of copper oxides, but this should not be a drawback when the alternative is to waste the copper present in low grade ores or in already

processed material. Research on bioleaching is yielding more efficient microorganisms whose physiological properties are being studied. The engineering aspects are also being investigated to assure abundant bacterial growth and homogeneous acid irrigation.

Chile is one of the world's leading countries in this novel application of BT. Copper accounts for 45% of Chilean exports, with a total production of about 5.5 million tons per year (the world demand is 18 million tons). Of these, about one third is produced by hydrometallurgy, a third of which is assisted by bacteria. In 2002, the state-owned Codelco-Chile, the world largest copper company, in conjunction with Nippon Mining & Metals Co Ltd, created BioSigma. The mission of this new public-private joint venture, which also received support from the Chilean Genome Program, is to formulate sustainable BT to exploit low grade mineral resources and other secondary material through *in situ* mining, that is, without the need of pirometallurgy. The company has identified and patented three new bacterial strains and has sequenced their corresponding genomes. Last year, these bacteria were inoculated into a 50,000 ton heap to produce the first copper cathode utilizing technology developed by BioSigma. It is still too early to report if BioSigma will accomplish the goal of replacing pirometallurgy by a more cost efficient process, but this may become another paradigm-shifting example of a successful BT developed in a non-industrialized country.

Sound knowledge instead of ideology or myth must be the criterion driving the adoption of new technologies

Two BT applications that are deemed to have a significant impact in developing nations are causing severe controversy throughout the world. They are the production of biofuels and the cultivation of genetically modified crops. They are particularly suited to illustrate that when there are uncertainties regarding the social benefits of a particular innovation, decision making must be based on scientific knowledge rather than on ideology or myth. Unfortunately, the latter has predominated in the discussion of these two relevant issues.

Let us first analyze the case of biofuels. The growing demand of energy for heating, transportation and industrial activities is causing a steady increase in oil consumption. Worldwide, countries are striving to diversify their energy sources, not only to cope with the unstable price of oil, but also to reduce greenhouse gas emissions from fossil fuels. Just to mention an example, in 2005 the USA consumed 140 billion gallons of gasoline plus diesel

just for transportation and the vehicles burning these fuels pumped out more than 308 million metric tons of carbon into the atmosphere[4].

Many think that the use of biofuels will significantly help to mitigate both problems. They can be blended up to 10% with gasoline with no damage to conventional engines. In some places there is also the alternative of an E85 blend, consisting of 85% bioethanol and 15% unleaded gasoline, although this mix requires adapted engines. On the other hand, combustion of bioethanol or biodiesel utilizes carbon that is being recycled by photosynthesis. Therefore, biofuels appear to be an attractive option, although the situation may vary significantly among the different countries.

The generation of energy through traditional BT is gaining impulse. In 2006, the USA produced 4.5 billion gallons of bioethanol from corn kernels and by the end of 2008, the production capacity is expected to reach 13 billion gallons. The process involves a liquefaction step to solubilize the starch, an enzymatic treatment to breakdown this polymer, followed by yeast fermentation of the resulting sugars[5]. This trend is likely to continue due to a series of tax incentives and proper legislation. On December 2007, President Bush signed into law a new energy bill that requires the production of 36 billion gallons of renewable fuel by 2022, thus increasing the target defined in The Energy Policy Act of 2005 by nearly five fold. The new law establishes that 15 billion gallons may come from corn ethanol, with the rest mandated to come from sources such as lignocellulosic crop waste, switchgrass and biodiesel.

However, with the present production process, some major difficulties must be resolved to allow biofuels to meet their expectations. Ethanol contains two-thirds of the British thermal units (btu) that are present in the same volume of gasoline. Therefore, even though the cost to convert plant matter into one gallon of ethanol is below the price of one gallon of gasoline, drivers will have to pump more ethanol to reach the same distance. Another drawback is the requirement of natural gas for the distillation of alcohol after the fermentation process. With the current industrial process, production of one gallon of bioethanol (80,000 btu of energy) requires about 36,000 btu of natural gas. The high demand has pushed the price of gas to levels that are economically inconvenient and some producers in the USA are now using coal, a solution that does not seem appropriate when the aim is to lower the greenhouse emissions. Other stages that require energy in the production of bioethanol are the chemical synthesis of fertilizers, the harvesting of the corn

[4] Editorial. *Nature Biotechnol*. 24, 725, 2006.

[5] Angenent, L. T.: "Energy biotechnology: beyond the general lignocellulose-to-ethanol pathway." *Curr. Op. Biotechnol*. 18, 191-192, 2007.

or sugarcane and the transportation of bioethanol to the market. According to a recent estimate by the American Institute of Biological Sciences, in the USA the production of ethanol from starch corn yields only 10% more energy than the amount required to produce it.

Another area of debate has been the greenhouse benefit of bioethanol. Some argue that the high consumption of natural gas makes it only marginally better than gasoline and that if this natural gas is replaced by coal, there is no advantage at all. Adding to this dilemma is that the heavy use of nitrogen fertilizer in growing corn leads to significant emissions of nitrous oxide, itself a potent greenhouse gas. On the other hand, some studies have shown that converting forest and grassland to new cropland to replace the grain diverted to biofuels has a net effect of increasing the emission of greenhouse gasses[6,7]. There are also drawbacks related to the alternative use of corn. Corn is presently used for human food and animal feed and its deviation to produce bioethanol has led to an increased price of corn-derived products and as a consequence the cost of meat has elevated as well. But even if the total corn crop in the USA were devoted to bioethanol production, it would only serve to supply 7% of the fuel consumed by its vehicles. In a similar vein, a recent study indicates that 10% substitution of petrol requires 43% of cropland area[8]. These shortcomings have led the OECD to declare that biofuels offer a cure that may be worse than the disease.

All these factors call for the exploitation of lignocelluloses rather than starch as a source of fermentable sugars. Lignocellulosic raw materials are by far more abundant than conventional agricultural feedstock and therefore they minimize the conflict of land use for energy instead of food or feed. Lignocelluloses form the stalk of the corn plant, the straw of grains, the biomass of some fast growing grasses and the residues of the wood industry. Thus, lignocelluloses are produced with a much lower consumption of pesticides and fertilizers than a traditional agricultural crop. Unfortunately, since solubilization of fermentable sugars from lignocelluloses is much more difficult than from starch, production of bioethanol from them is at present economically unfeasible. Research is required to overcome this limitation. The main objectives are the depolymerization of both the cellulose and hemicelluloses, the efficient fermentation of the sugar mixture and the cost-

[6] Searchinger, T.; Heimlich, R.; Houghton, RA.; Dong, F.; Elobeid, A.; Fabiosa, J.; Tokgoz, S.; Hayes, D.; and Yu, T-H.: "Use of U.S. croplands for biofuels increases greenhouse gases through emissions from land use change." *Science* 319, 1238-1240, 2008.

[7] Fargione, J.; Hill, J.; Tilman, D.; Polasky, S.; and Hawthorne, P.: "Land clearing and the biofuel carbon debt". *Science* 319, 1235-1237, 2008.

[8] Righelato, R. and Spracklen, DV.: "Carbon mitigation by biofuels or by saving and restoring forests?" *Science* 317, 902, 2007.

efficient use of lignin. It is widely known in the pulp industry that lignin burns well and in several mills it is used to generate electricity. Net emissions of carbon dioxide per mile driven on cellulose ethanol would decrease abruptly if lignin-derived electricity could displace coal or natural gas as the power source. There are already significant advances to integrate the process and reduce capital costs. Microbial strains have been metabolically engineered to ferment both types of sugars. Process integration has also been attempted with the simultaneous depolymerization and fermentation of the polysaccharides (SSCF process). Currently, scientists are attempting consolidated bioprocessing (CBP), which involves the engineering of microorganisms that would produce both the hydrolytic enzymes and ferment all the sugars.

Whether lignocellulosic ethanol will ever reach the market is a matter of debate. It will depend on the price of oil, the success of the research efforts and other factors, such as the mentality and aims of the USA automotive industry. However, this objective that seems so critical for the USA may not be so essential for other countries. In 2006, Brazil produced a similar volume of bioethanol (4.5 billion gallons) by direct fermentation of sugarcane sugar. The energy balance of this process is much more favorable than the one that uses starch. The bioethanol program in Brazil was initiated as a result of the oil crisis of 1973 and has experienced up and downs that have followed the price of oil. In 2004, the first automobiles with Flex engines were sold. These cars run with pure ethanol, with pure gasoline, or with any mixture of the two. In 2006, 73% of all new cars sold in Brazil had Flex engines. The use of bioethanol is stimulated by its price, which can be 40% lower than that of gasoline due to the availability of raw material, the relative simplicity of the process and the low cost of labor. There seem to be no obstacles for the continuing development of this strategic bioindustry in Brazil. The country is presently reducing its petroleum imports by 200,000 barrels per day, with the added bonus that bioethanol production generates employment and there is plenty of crop land for sugarcane plantation.

The field of biofuels also includes the production of biodiesel. Biodiesel refers to a mixture of organic esters comprised of animal or vegetable oils. Biodiesel can be used to replace petroleum diesel, in the same way as bioethanol replaces gasoline. The raw material is mainly rapeseed. In the European Union, bioethanol is not an overly attractive option, due to the lack of land. However, production of biodiesel in 2005 was 3.2 million tons, 65% higher than in 2004. The European Commission has recently released a plan targeting biofuels for 10% of transportation fuels by 2020. Tax exemption policies set up in Germany, Spain, the United Kingdom, Italy and France, are aimed at this implementation.

Biodiesel production is interesting because it does not necessarily compete with the cultivation of food. It can be produced from some peculiar plants, from algae and even from waste. An example of the latter is the announcement of Mc Donald's to convert all its UK distribution trucks to run on biodiesel made from its huge stock of spent cooking oil. There is also the promising case of the plant *Jatropha curcas*[9], a wild specimen that has been used for years as a source of lamp oil and soap. Its yield in liters of oil per hectare (1,300) compares favorably with those of rapeseed (1,100) and soy bean (400). This plant grows well in non-arable wasteland and its cultivation can halt soil erosion, increase soil water storage and thus transform infertile soil into productive land. In 2003, India's Planning Commission recommended the planting of 500,000 hectares of jatropha and if the biofuel program shows progress, to increase the planting to 12 million hectares. The rail service has already planted a million seedlings along its tracks for future consumption. China also plans to have a similar surface area planted with jatropha by 2010. There is, however, one major concern: the plant has never been domesticated and not much is known about its biology. Time will tell if the expectations on this resource are fulfilled.

As mentioned previously, another BT application that has raised worldwide controversy is the genetic engineering of plants. However, in spite of the ongoing debate, the global market value of genetically engineered crops (heretofore referred to as biotech crops) in 2007 was estimated to be US$ 6.9 billion, representing 20% of the global commercial seed market. The same year, the global surface of biotech crops reached 114.3 million hectares[10]. At present, there are 23 countries with more than 50,000 hectares planted, whereas an additional 29 countries have granted approvals for their import and consumption. Herbicide tolerance transferred into soybean, maize, canola, cotton and alfalfa covers 72% of the global biotech cropland. Another 19% corresponds to a trait naturally encoded in a bacterial gene that confers resistance to insects, whereas 13% of the land is planted with crops stacked with traits for both insect and herbicide tolerance. Although the USA and Canada account for about 60% of the transgenic crops, developing nations are also embracing this technology. Among these, Argentina, Brazil, China and India are the most noticeable cases, with 33% of the total planted surface of biotech crops. However, recent studies also show that profitability varies from country to country or even among regions of the same country[11]. This variation is due to institutional factors such as local legislations (or lack of),

[9] Fairless, D.: "The little shrub that could-maybe". *Nature* 449, 652-655, 2007.

[10] Most of this data was obtained from www.isaaa.org.

[11] Raney, T.: "Economic impact of transgenic crops in developing countries." *Curr. Op. Biotechnol*. 17, 174-178, 2006.

environmental regulations and trade and intellectual property rights. The paradoxical situation of Chile in this respect illustrates the need of proper legislation. Chilean farmers can grow genetically modified crops for seed export and can import biotech food and feed, but they cannot plant biotech crops for local consumption.

The European Union has been traditionally known for its lack of enthusiasm for biotech crops. Some years ago, the United States complained to the World Trade Organization that European reluctance to accept them was mere protectionism. This attitude seems to be slowly losing ground, although with small plantations. There are now 6 out of the 25 EU countries that grow insect-resistant maize, the only currently approved biotech crop. Next in line awaiting authorization are, among others, two maize cultivars which are engineered to be resistant to both pests and herbicides, but these have been kept on hold by the EU environment commissioner's office.

One of the most interesting features about biotech crops is that there are more than 10 million farmers involved in their cultivation. About 90% of them are in China, India and the Philippines. The rapid growth in the number of farmers reflects the fact that they are obtaining benefits that may include lower consumption of pesticides, lower production costs and better yields. This contradicts the contention that these products benefit only farmers that can take advantage of large-scale economies[12]. A recent survey[13] showed that the total profit for biotech farmers in the last decade reached US$ 27 billion, a sum equally distributed between developing and industrialized countries. The decrease in pesticide use in the same period was 224,000 tons, with the concomitant environmental benefit derived from the lower use of fossil fuel employed in their production. It is conceivable that better crop yields will free more land for plants devoted to biofuels, thus producing further environmental benefits.

Another key challenge in benefiting biotech farmers from developing countries is to improve the research capacity of these nations. The previous green revolution that increased farm productivity by conventional methods of selective breeding was led by researchers from academic and public sector institutions. In contrast, a significant fraction of the new gene revolution is driven by multinational corporations that patent their findings. This is a key issue, because the interest of the private companies relies mainly in highly profitable products. In some cases, the higher costs of genetically modified

[12] Raney, R. and Pingali, P.: "Sowing a gene revolution."*Sci. Am.* 104-111, sept. 2007.

[13] Brookes, G. and Barfoot, P.: "GM Crops: The first ten years - Global socio-economic and environmental impacts." P.G. Economics, 2006.

seeds can be compensated with a lower consumption of pesticides and/or with higher yields. However, these products may not satisfy the needs of some less developed regions of the globe. For example, some countries may require an improvement in the nutritional value of crops that are relevant to their diets, or an increase in the low yields stemming from poor quality soils. Currently, China develops its own biotech crops, whereas Brazil, India and South Africa are showing progress in this respect, although not presently producing commercial crops.

There is still a further ingredient for the success of this modern agricultural revolution throughout the globe, namely, public perception. This is a highly relevant issue for this application of BT, since we have witnessed situations of extreme intolerance, such as the destruction of biotech cultures and violent aggressions against fast food restaurants that utilize genetically engineered modified ingredients. Disagreement should not be unexpected, since it is a well known fact that people tend to be reluctant to change. When the Spanish brought the potato to Europe in 1570, nobody was willing to eat it. Undoubtedly a mixture of superstition and myth, it was first thought to be toxic and then to cause leprosy. Paradoxically, the potato omelet is today one of the most typical dishes in Spain. Very often we listen to politicians, journalists, environmentalists and the general public to debate about genetically engineered crops, with arguments that most of the times are devoid of scientific support and loaded with subjectivity. Some say that the introduction of foreign genes (and promoters) may activate viruses that are dormant in the plants. Others argue that the biotech foods are toxic, cause allergies or increase the resistance of the consumers to antibiotics. Some even assert that biotech crops will promote gene flow into related crops or wild plants, or that they will cause an increase in the use of pesticides and herbicides, or that they affect biodiversity, etc. Although *a priori* these accusations could have some rational support, none has been scientifically demonstrated. Claims related to allergies or toxicity are especially irrelevant when the edible product derived from a biotech crop is indistinguishable from the conventional one, as it is the case of sugar or oil.

It is indeed reasonable to take some precautions before authorizing a new biotech crop for large scale plantation and commercialization, but this should be done with non- obstructive legislation and regulations. For example, if there is concern about a possible impact on human health or the environment, tests should be conducted following standard protocols. Then, a decision can be adopted based on scientific evidence, not on prejudice, emotions or myth. In this regard, the public statements released by the Science Academies of the USA, Brazil, China, India, Mexico, United Kingdom,

Chile, The Vatican and The Academy of Sciences for the Developing World (TWAS) could serve as suitable guidelines.

The case of rice is most appropriate to further illustrate the importance of public perception. As it is well known, this crop is an essential component of the diet in various developing countries. Two years ago, Iran was the first country to approve the commercial growth of a variety of pest-resistant transgenic rice for human consumption. To date, China has been reluctant to do it, fearing a negative reaction from countries that import Chinese rice. There is also the case of Golden Rice, enriched in beta-carotene to make up the deficit of vitamin A in malnourished populations. Vitamin A plays a vital role in various physiological processes, such as sight, growth, normal development and immunity to disease. Every year, half a million people, mainly children, become blind as a consequence of vitamin A deficiency, and fifty per cent of these may die within a year of becoming blind[14]. Originally developed in Europe in 2001 with genes from plants and bacteria, Golden Rice was later upgraded with a gene from maize that led to a 20-fold increase in the amount of vitamin A precursor. A recent study[15] has shown that 100 g of Golden Rice provide the recommended daily intake of vitamin A for a preschool child. In turn, a report by the World Bank claims that the potential welfare improvement for South Asian countries that could adopt Golden Rice would be in the range of billions of dollars annually[16]. The so-called Humanitarian Golden Rice Network led by Ingo Potrykus has made the rice freely available to research centers that are developing locally adapted varieties in several countries. However, in none of them has Golden Rice yet been authorized for human consumption. Some lack the proper legislation or biosecurity procedures, whereas others still have to test environmental and human health safety. It is expected that local varieties of Golden Rice will be released in a couple of years. At the other side of the ring, Golden Rice has had foes from the beginning. Detractors say that the possible benefits of Golden Rice have been overestimated, whereas others claim that there are more economic ways to combat vitamin A deficiency. This discussion is still taking place. Whatever its outcome, nobody could argue that consumption of a Golden Rice that has passed all the safety hurdles is better than traditional rice for human health, especially in poorer countries.

[14] Mayer, JE.: "Golden rice, golden crops, golden prospects." *Rev. Colomb. Biotechnol.* IX, 22-34, 2007.

[15] "Nutritional and safety assessments of foods and feeds nutritionally improved through BT: case studies". Executive summary of a task force report by the International Life Sciences Institute, Washigton, DC. Doi: 101111/j.1750-3841.2007.00579.x.

[16] Anderson, K.; Jackson, LA.; Pohl Nielsen, C.: "Genetically modified rice adoption: Implications for welfare and poverty alleviation." Centre for International Economic Studies. Discussion Paper 0413,2004.

BT and bioethics

Both genetic and cell manipulation of living organisms have bioethical implications. When conducted with microorganisms, plants and animals, they must be performed following the corresponding safety guidelines. These consist of standard protocols that have been designed to prevent harm to human health, to safeguard the well being of genetically modified animals and to protect the environment. However, bioethical concerns are particularly relevant when they involve the manipulation of human genes and cells. Although these matters are not related to the biotech applications described previously, their profound social relevance leaves no room for moral indifference.

In recent years we have witnessed a harsh controversy regarding the use of embryonic stem cells to alleviate various diseases. Although this may be a promising therapeutic approach that brings hope to millions of patients throughout the world, it requires the destruction of human embryos to obtain the cells. These embryos may be leftovers from *in vitro* fertilization procedures, or may be created solely for obtaining stem cells. The latter adds further complications, such as to find who will supply the eggs, how might the suppliers be paid and what would their rights be, if any. Even worse is the possibility of assembling human embryos by means of nuclear transplantation, an euphemism often employed to avoid mentioning the word cloning. In all circumstances, the human embryo should be afforded proper respect, since it is human life in its earlier stages of development. How can a treatment which claims to save human lives, be based upon the destruction of human life in its embryonic state? This utilitarian perspective, implying that the end justifies the means, is logically and morally contradictory, as is any production of human embryos for the direct or indirect purpose of experimentation or eventual destruction[17]. This is not a matter concerning a particular religion. It is simply an innate intuition that tells us that there is something special about being human. We can recognize that this fundamental difference is related to our rationality, which constitutes the bases of human dignity. This dignity is manifested in an ethical conscience, in the capacity to love, to comprehend and to create. It is also made explicit in the ability to transmit cultural values, in the right to freedom, to autonomy and to intimacy. As stated by Kant, each person is an end in itself. Fortunately, there are alternatives to the use of embryonic stem cells. These are stem cells derived from adult tissues or from tissues superfluous to normal

[17] Address of John Paul II to the members of the Pontifical Academy of Sciences, 10 November 2003.

fetus development. Although these cells appear to exhibit less plasticity than embryonic cells, published clinical studies show that adult stem cells have treated more than 60 diseases in human patients. On the other hand, two groups have recently show that it is possible to reprogram human skin cells into pluripotent cells[18,19]. Scientists, therefore, should be encouraged to focus their future research in the use of non-embryonic stem cells, which have already shown to be therapeutically beneficial.

Similar reasons of human dignity make a strong case against the practice of human gene manipulation. First of all, the decision regarding an irreversible change in the genotype that would be transmitted to future generations would be taken by people who will not be affected by these changes. In addition, it would necessary imply the manipulation and experimentation of *in vitro* derived embryos. It would also pose unavoidable risks due to mutations or alterations in the regulation of gene expression. Moreover, it would compel the pre-implantation screening of the embryos and sooner or later it would inevitably derive in those wanting to do genetic enhancement (eugenics). There is, however, an application of genetic engineering in humans that is directed to somatic rather than to germ line cells. Therefore, the new trait is not transmitted to the descendants. It is called gene therapy and consists in the insertion of a foreign gene into the patient's tissues in order to treat a disease. Human gene therapy is not devoid of bioethical connotations. However, they can be approached with criteria similar to those of traditional therapies. At present there are about 1,300 registered patients throughout the world that are diagnosed with cancer, a monogenic disease or other ailment, that are being treated by gene therapy. It should be expected that this new approach to treat disease will succeed and spread around the globe.

The preimplantation genetic diagnosis method mentioned in the previous paragraph deserves further comments, because it evokes quality control applied to human reproduction. Before the advent of *in vitro* fertilization, genetic mutations could be diagnosed during pregnancy by taking samples from placental tissue or from amniotic fluid. In either case, fetal cells were analyzed for the presence of chromosome or gene abnormalities. If the fetus was found to harbor a genetic disease, abortion was the most

[18] Takahashi, K.; Tanabe, K.; Ohnuki, M.; Narita, M.; Ichisaka, T.; Tomoda, K.; Yamanaka, S.: "Induction of pluripotent stem cells from adult human fibroblasts by defined factors". *Cell.* 131, 861-872, 2007.

[19] Yu, J.; Vodyanik, MA.; Smuga-Otto, K.; Antosiewicz-Bourget, J.; Frane, JL.; Tian, S.; Nie, J.; Jonsdottir, GA.; Ruotti, V.; Stewart, R.; Slukvin, II.; Thomson, JA.:. "Induced pluripotent stem cell lines derived from human somatic cells." *Science* 318, 1917-1920, 2007.

common choice for preventing birth of an abnormal child. Upon the development of the *in vitro* fertilization techniques, it became possible to screen cells from the embryo before its implantation into the uterus. This procedure can be performed with one or two cells (blastomeres) extracted with a micropipette from an eight-cell stage embryo. The mammalian embryo can easily replace these cells and presumably their removal presents no threat to normal development. The presumptive normal embryos are selected for implantation into the uterus, whereas the presumptive defective embryos are discarded. For most people, there seems to be no ethical obstacle in this action.

It is estimated that every year 1,000 embryos are selected by preimplantation diagnosis[20]. Aside from the fact that embryo disposal reflects a complete lack of respect for human life, the benefits of this procedure are far of being demonstrated. Although some claim that embryo screening has decreased the proportion of woman undergoing miscarriage, others are critical of the data supporting this evidence. This controversy may arise from the fact that researchers have found that about one half of human embryos produced *in vitro* are composed of a mixture of normal and abnormal cells (mosaicism). Recent studies show that these embryos tend to self correct, spontaneously eliminating the cells with genetic abnormalities. This would imply that embryos that are being thrown away for being prone to genetic diseases would otherwise develop in healthy conditions. But there is still another apprehension with preimplantation diagnosis, which is whether it constitutes a safe practice for the developing embryo. The current paradigm states that all cells in very early embryos are equivalent and therefore it should not matter which of them is removed. However, some groups have shown that some cells are predisposed to contribute in a specific way to future tissues. Unfortunately, it may take years to verify the real consequences of this drastic procedure in human development.

Concluding remarks

As powerful as it may seem, BT should not be considered as a panacea that will cure all our ails. BT is a robust tool that offers innovative options for the production of goods in human and animal health, the food and feed industries, agriculture, forestry and mining, among virtually all applied fields. It also offers the possibility of new energy sources, along with novel exploitations of natural resources and the treatment of pollutants. However,

[20] Goldman, B.: “The first cut.” *Nature* 445, 479-480, 2007.

the convenience of a particular application should be analyzed jointly in its merit, in its bioethical and political context, and in comparison with other options. Agriculture offers a good example to illustrate this criterion. In some cases, growth of a genetically modified crop may be the right option. In many others, however, traditional agriculture will continue to be the best choice. Moreover, the market will even tell if there will also be room for organic agriculture.

The rapid development of modern BT has opened scenarios that had not been predicted. We are now confronted with situations that summon our bioethical sense and that compel us to act with responsibility. An education and change in public perception on BT is required to curb opponents that have in many instances appealed to violence to impose their views, yet who paradoxically are often in favor of destroying human embryos, revealing a bioethical double standard that hinders an objective dialogue. Continued dialogue is paramount, as is the implementation of universal regulations and guidelines. Furthermore, ethical, political and philosophical debates on the potentials and consequences of biotechnology should be ongoing to avoid the misgivings in current legislation, which at times have the appearance of closing the stable door after the horse has bolted.

Although in most cases derived from advances made in industrialized nations, lower costs in food and pharmaceuticals could significantly impact developing countries. However, it is strategically important that developing countries also set up policies to reach autonomy in the application of biotechnologies and thus sustain their own advancement. These policies should include the support of research programs and the establishment of overseas partnerships in both the public and private sectors. Now and in the future, the overall aim is that biotechnological processes are more cost effective and environmentally friendly than traditional methods.

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