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AGRICULTURAL BIOTECHNOLOGY TRENDS AND CHALLENGES[1]

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Abstract

The main objective of this paper is to assess the leading edges of today's knowledge in agricultural biotechnology at the global scale, and offer some recommendations on the possible niches of the Philippines. Until recently, biotechnology is neatly classified as agricultural (including forestry and aquaculture), health, industrial and environmental. Presently, however, a great revolution is going on. Agricultural biotechnology is invading the other fields of biotechnology! We can call this the third agricultural revolution. The first revolution started the process we now call civilization 10000 years ago; the second (the Green Revolution) saved civilization from hunger about 40 years ago. The third hopes to save us from the problems created by the first and second revolutions and provide the material needs of future generations in a sustainable manner.

The scope of agriculture is now being extended from provision of basic needs, namely, food, fiber and clothing to include needs of modern civilization such as energy, materials, drugs, and industrial products such as enzymes. The definition of agricultural crops is being extended to include not only higher plants, but all photosynthesizing organisms. Techniques traditionally used for industrial scale culture of bacteria and fungi are being applied for single cell, tissue and organ cultures of higher plants and other photosynthesizing organisms. Thus, we are looking forward to a new generation of biofactories and production systems using photosynthesis as the main engine. These biofactories will produce traditional and non-traditional products cheaper, faster, safer and better. It is an exciting future with a lot of promises but many challenges and unknown perils, too.

The niche for the Philippines is dictated by the reality that its land area, the traditional basis of agriculture is limited. In addition, its climate is generally less favorable for traditional agriculture than many other environments. On the other

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hand, the Philippines has a huge surplus of unemployed manpower, sunshine and water. Review of recent literature suggests the following leading edges suitable for the Philippines for scientific and technological development in the field of conventional and modern agricultural biotechnology: 1) new agricultural crops that are less susceptible to the vagaries of local climate and limitations of arable land, 2) new approaches for recombinant DNA technology, specifically plastid engineering; and 3) bioreactors and less sophisticated production systems using higher plant cells and organ cultures, and other photosynthesizing organisms such as mosses and algae.

Scientific literacy is a prerequisite for the third agricultural revolution. A scientifically literate nation will formulate policies that will encourage innovation, deploy its best minds to the service of science and technology, and create a public that is receptive to new ideas. Even as we look to the future, the struggle for public acceptance of the third agricultural revolution is taking place today. There are existing biotechnologies waiting to be used, such as transgenic crops, livestock, forest trees and fishes. These will not prosper if public reaction and corresponding government regulation is guided by imagined risks rather than demonstrated benefits. The paper argues for a system of regulation that will achieve an appropriate balance between the need to assure the public of the safety of agricultural biotechnology and the imperative to explore new technology for solving the problems of modern living.

Keywords: agricultural biotechnology, biotechnology, green revolution, transgenic crops, recombinant DNA

Introduction

The future of agricultural biotechnology is not likely to be limited to transgenic crops grown in the field for clothing, feed and food. Energy, fuels, chemicals and fibers, products that have been traditionally obtained from the petrochemical industry, are likely to be an equally important objective for agricultural biotechnology in the near future, and transgenic crops are expected to make an important input to these goals.

Transgenic crops will not necessarily be grown only in the field, and it will not necessarily involve culture of field and horticultural crops by conventional farmers. Cell and tissue cultures of higher and lower plant forms will find novel uses in pharmaceutical, industrial and environmental applications. Plants are simply more flexible, faster and safer as "biofactories" of useful molecules that were traditionally produced using chemical processes, or biological processes using microorganisms and animal cell systems as platforms. Transgenic livestock and fish will take a little more time to reach acceptance, but lessons learned from the

transgenic crops will contribute to the understanding and solution of unique problems in these products.

There will be less controversy in the future as science clarifies the various safety and environmental concerns that dominate today's debate, technology becomes more predictable and less prone to unintended effects, and superstition becomes less of a factor in policy making. Further, the sheer magnitude of problems associated with improving the quality of life of a growing world population will finally convince the world that the imagined risk of genetic engineering is greatly outweighed by its demonstrated benefits.

There were initial concerns that the benefits of agricultural genetic engineering would not benefit the poor and disadvantaged sector of society. We had the same concern when such common devices as the motor vehicle, radio, television, computers, and cell phones first came to commerce. Only the rich could afford them then. But it took less than 50 years for the motorcycles and automobiles to become available for mass consumption, less than 30 years for the computer to reach the farthest end of the planet, and less than 10 years for the cell phone to reach the hands of the poorest sector of society. Today, transgenic corn, soybeans and cotton are grown by more poor farmers worldwide than rich farmers, only 10 years since their first introduction in the USA. It is only a matter of time before the benefit of transgenesis spreads to other crops, livestock, forest trees and fish. Improved technology will be a crucial factor, as it was in the case of cell phones and other modern gadgets.

In this paper, we are going to show where science and industry are leading agricultural biotechnology and agriculture in general, and how much safer, more predictable, faster and cheaper the basic needs of man are being met by genetic engineering. Towards the end, we are going to show how a poor country such as the Philippines can benefit from agricultural genetic engineering biotechnology.

Scope of Agricultural Biotechnology

Not too long ago, agriculture was so simple. It simply meant production of agronomic and horticultural crops, on one hand, and poultry and livestock on the other hand. Agriculture includes to some extent, primary processing such as making copra or drying of coffee beans. Then agroforestry came along, together with the concept of industrial tree plantations. The confusion started. Is this agriculture or forestry? Then came aquaculture and integration of farming and fishery, seaweeds. Are "weeds" not supposed to be the concern of plant agriculture? Are not the principles of aquaculture the same as agriculture? After all, fish also need to be fed and protected from pests and diseases, like livestock and plants. Fish breeding is also selection and generation of variability, in the same way that plant breeding is. Government solved this confusion neatly by putting fishery in the Department of Agriculture, but the status of agroforestry and industrial tree plantations remain contentious.

At the basic level, there is less confusion. Take courses in basic agriculture, forestry and fishery today and you will likely get the same lessons in physiology, biochemistry, ecology and genetics; as well as nutrition, health care, and breeding. The case studies will be different but the principles will be essentially the same.

At the most basic level, there is no confusion. Life is chemistry, guessed Jan Batista van Helmont in 1648. Today we know that this is not only true, but in addition we know that the chemistries of all living things are essentially the same. This has been the fundamental assumption, repeatedly proven, in genetic engineering. Take a gene from a bacterium, and with only a few tricks, it will function in plants, or any other living form for that matter. This is because bacteria and other living forms share many biochemical processes in common. When the human genome was completed, one of the surprises was the discovery of some 100 or so DNA sequences that look like bacterial genes. We share about 40% of our genes with plants; and 98.5% with chimpanzee.

Genetics is a great simplifying discipline, but genetic engineering does the exact opposite. It adds a different level of confusion to that caused by new disciplines such as agroforestry or seaweed farming. When you genetically engineer a corn plant using a bacterial gene and techniques in microbiology, is this microbiology or agriculture? At least on this point, there seems to be a consensus. It is agricultural biotechnology, perhaps because the use of corn is not altered. It is still used for food or feed. Or perhaps it is because one gene from a bacterium does not convert the corn into a bacterium. But when you genetically engineer a corn plant to produce a drug, is this biopharma or agricultural biotechnology? When you genetically engineer a pig to produce organs that can be used for people, is this health biotechnology or agricultural biotechnology?

These questions may sound trivial, but they raise serious challenges to the way we see the biological world, organize, and transmit knowledge today. In the same manner that genomic information has challenged classical taxonomy, genetic engineering poses a challenge to traditional ways of organizing knowledge and technology. This obviously is not a problem for industry, which does not recognize boundaries; but it is a great problem for academe and government; especially for academe, which must reflect new ways of organizing knowledge in its academic programs and organizational structure.

Beyond all these confusions is the fact that traditional agricultural crops and livestock are now expected not only to produce food, feed and fiber; but also energy, fuels, chemicals and materials; even drugs. The need for new crops species to supply sufficient quantities of these needs in a sustainable manner has led to cultivation of traditional forest species. Principles and practices in modern agriculture are being applied to industrial tree plantations and aquaculture. Agriculture is expanding and so is agricultural biotechnology. We do not know where it will end. I have no doubt that many of you will disagree, but this is the premise of my subsequent presentations.

Making Agricultural Biotechnology More Predictable and Safer

1. New tools for documenting the impact of genetic engineering at the molecular level

As a new technology, genetically modified crops understandably create anxiety and fear to the average person. This fear is encouraged by popular movies such as genetically modified fish, snakes, and even ants that eat people. Indeed, fear of the unknown is the element that is being exploited by those who would like to discredit GMOs for whatever reason.

Research has developed new tools that serve to illuminate many of the uncertainties and so-called unintended consequences of genetic modification. One of these tools is molecular profiling, which allows comparison of gene expression of GMOs with non-GMOs at the global (entire genome) level, unlike before when it was only possible to look at the action of one or a few genes at a time. The products examined may be RNA, proteins or secondary metabolites. The limitation of the old method is that it is not possible to determine if the transgene has influenced other genes. It is also not possible to determine in a direct way if novel proteins (in addition to the transgene product) are somehow produced. This limitation gave way to speculations that genetic modification could alter genes that are not meant to be altered, or otherwise result in unspecified interactions among genes leading to the production of new molecules that can be harmful to the environment or human health.

Molecular profiling and microarray analysis have been done with *Arabidopsis*, a model plant, wheat, and potato in recent literature. In the case of *Arabidopsis*, the ATH1 GeneChip from Affymetrix was used to search for transcriptome changes associated with the strong expression of transgenes. From this work, no change in the transcription pattern of approximately 24000 genes could be associated with the transgene expression. The authors concluded that the transgenic and non-transgenic plants were equivalent in their global patterns of transcription.[1]

In the case of wheat, comparison was made between wheat that has been transformed of a phytase gene, and the untransformed version of the same line. A 9K wheat cDNA microarray was hybridized to fluorescently labeled cDNA from developing seeds of the experimental materials. Results of this comparison were validated using real time PCR. The conclusion was that the phytase gene had no significant effects on the overall gene expression patterns.[2]

In the case of potato, a comparison was made in the pattern of proteins among eight GM lines, the parent cultivar Desiree, and a line that had undergone tissue culture only. Only nine out of 750 proteins showed statistically significant differences among the GM lines and the controls. No new proteins unique to the GM lines were observed and there was no evidence for any major change in protein patterns. In addition, the study showed that the differences among non-GM cultivars were much greater than the differences among the GM lines.[3]

Molecular profiling has its own limitation. First, it is not possible to cover all the products of gene action. While present technology now allows a fairly exhaustive coverage of DNA and RNA, a similar coverage of proteins and metabolites is not yet practically possible. In the first place, the profiles of proteins and metabolites, like that of cDNA and mRNA, can be altered by environmental and developmental factors. Secondly, the total number of chemical substances produced by plants is simply so enormous (estimated to be 100,000–200,000), and any single plants would have 5,000–10,000[4]. There is not one analytical method today that can identify and quantify this diversity of substances. But the most important limitation of molecular profiling is the difficulty in interpreting the biological significance of differences in molecular profiles.

2. New tools reduce the element of uncertainty and perception of risk in genetic engineering

a. Selectable markers

The most common marker used in production of current commercial transgenic crops is the antibiotic resistance gene. Although this method has been exhaustively studied and believed to be relatively safe, there is a persistent fear of the antibiotic gene being somehow transferred to human pathogenic bacteria.[5] The following alternative selectable marker genes can be used in future constructs:

- Antibiotic resistance gene of plant origin as an alternative to the *nptII* gene from *E. coli* which is popularly used. This concept was demonstrated using *Atwbc* 19, a gene obtained from *A. thaliana*, and used as a selectable marker in transgenic tobacco.[6]
- Many more novel selectable marker genes that do not involve antibiotic resistance were described by Bajaj and Mohanty 2005.[7]

b. Promoters

Another commonly raised concern regarding the current set of commercial transgenic crops is the use of 35S CaMV promoter, which was obtained from the cauliflower mosaic virus. This type of promoter results in gene expression in practically every tissue of the plant all the time. The level of gene expression is determined partly by the promoter used in the construct. In the case of 35S CaMV promoter, duplication of some sequences and addition of enhancer regions were done to improve gene expression. Critics fear that this promoter may somehow be integrated in cells of the human intestine if the transgenic crop is used for food, and cause unintended effects.[8] However, the more important issue regarding constitutive promoters, in general, is that their use is theoretically a waste of the plant's energy. The ideal promoter is one that will be active only when and where it is needed, and will result in optimum level of gene expression.

Concerns about the "foreign" nature of first generation promoters motivated the use of constitutive promoters obtained from plants such as rice *actin1* and

maize *ubiquitin* promoters, which are widely used in monocot transformation.[9] In dicots, a number of endogenous constitutive promoters have been reported but they are not yet widely used. Lately, a new constitutive promoter from *Medicago truncatula*, designated *MtHP*, was claimed to direct higher levels of gene expression than 35S CaMV.[10]

A truly "clean" transformation system could be visualized as one that uses only DNA of plant origin. One approach is to use a plant-derived (P-) DNA fragment to replace the universally employed Agrobacterium transfer (T-) DNA , coupled with a method for negative selection against marker gene integration. This was used to produce marker-free and backbone free potato, which was claimed to be the first transgenic plants that only contain native DNA.[11] To complement this technique, the desired genes can be obtained from other species of plants of the same or different genera instead of obtaining them from other Kingdoms. Examples of these are Xa21 gene, which was transferred from a wild to cultivated species of rice and ferritin gene, which was transferred from soybeans to rice.

c. In planta transformation

Embryogenic and meristematic tissues are the usual materials used in plant transformation. They have the advantage of ease in handling large number of potential plants, ease in selection and they facilitate recovery of hundreds of transformed plants. However, they have one serious problem: they have to pass through tissue culture stage, including dedifferentiation and embryogenesis. This limits the scope of transformation because many species and varieties are recalcitrant to tissue culture. Further, the tissue culture process often produces mutations that may not only affect the transferred DNA, but give other undesirable plant characteristics leading to the rejection of the lines derived from mutants. In addition, significant epigenetic changes can also occur.[12] The net result is that a plant breeder needs to screen a large population of plants transformed with the same construct to find one that has the desired combination of simple DNA insertion, desired level and stability of gene expression and minimal mutation from tissue culture.

To avoid the problems associated with tissue culture, work on in planta transformation started with the model plant *Arabidopsis* in the late 1980s.[13] Work in the 1990s demonstrated the possibility of transforming seeds, seedlings and flowers of this model plant and subsequently in other species of Brassica such as pakchoi[14] and radish.[15] The technique was as simple as dipping, spraying, or pricking the seeds, seedlings or flowers with the *Agrobacterium* inoculum, growing the plant to maturity, and screening for transformants in the next generation. However, it was not until 2000 that the technique was successfully used in another non-Brassica plant species, *Medicago truncatula*.[16] Recently, in planta transformation of the model monocot species rice[17] was reported. All of these methods relied on the use of *Agrobacterium* as a vector.

d. Plastid transformation

DNA in plants is not solely found in the nucleus. It is also found in the mitochondria and in the plastids (such as chloroplasts, amyloplasts, and elaioplasts). Thus, the possibility of plastid transformation has been recognized and demonstrated in the case of algae in 1988[18], and subsequently in tobacco in 1990.[19]

Plastid genome transformation provides a solution to many of the difficulties associated with nuclear genome transformation. Among these are the problems of site-specificity, gene silencing because of high transgene copy numbers, and low expression levels or conversely, pleiotropic effects due to very high concentrations of foreign proteins in the cytoplasm resulting from the expression of the nuclear transgene (Daniell et al 2002). Plastid transformation benefits from a high frequency of homologous recombination, absence of gene silencing even at very high transgene expression levels, ability to introduce blocks of foreign genes in a single operon, and maternal inheritance (plastid genes are not present in the pollen).[20] The high levels of protein products that could be produced in the plastids, as well as the high quality of these proteins make plastid transformation ideal for many purposes, such as production of pharmaceutical products. The possibility for introduction of multiple genes in a single block simplifies the modification of biochemical pathways. Indeed, the use of plastid transformation for enabling plants to fix N and improving photosynthetic CO_2 fixation have been mentioned as possibilities in early literature.[21]

Nevertheless, the practical application of plastid transformation is fairly recent. A 2000 review by Bogorad noted that tobacco was the only crop in which fertile plants with plastid transgenes have been described. This is partly because many crop plants could only be regenerated using non-green embryonic cells (containing proplastids) rather than leaf cells (containing chloroplasts).[22] Problems such as retentibn of transgenes in the presence of untransformed plastids, and limitations such as lack of information on genome sequences have slowed progress. Moreover, there are problems associated with post-translational modification of chloroplast-derived proteins, thus this technology is limited to products that are active without modifications (Joshi and Lopez 2005). Lastly, among the methods used to transform plant chloroplasts, only particle bombardment (with its known limitations) has proven to be efficient.

Taken together, the new knowledge and tools would tend to reduce the element of uncertainty in the transformation process as well as on the quality and safety of the product. The in planta transformation systems could reduce the background mutation effects that tissue culture-based transformation systems used before are associated with, making the transformation process less disruptive to the plant genome. The discovery of plant genes, promoters, regulatory elements and selectable markers provides future biotechnologists the option to use these instead of "foreign" DNA. The availability of inducible and tissue specific promoters will be an added assurance that the gene products will only be expressed when

and where it is needed, unlike in the first generation GMOs. Gene targeting technology will reduce the uncertainty of the integration site of transgenes among other benefits. Finally, technologies such as plastid transformation provides a degree of assurance that pollen from transgenic crops will be free of transgenes. Indeed, the toolbox for plant genetic engineering has greatly enlarged as a consequence of persistent research.

3. New platforms for transgene expression

a. From microorganisms and animal cells to plants

Plant genetic engineering biotechnology is described today as having three phases. The first phase refers to engineering of input traits: those that benefit the farmer, such as insect resistance and herbicide tolerance. The second phase refers to engineering of output traits: those that benefit the consumers, such as Golden Rice and Vestive™ soybeans that contains a reduced level of linolenic acid. The third phase refers to the production of high value products such as antibodies, vaccines, therapeutic proteins, as well as industrial enzymes and secondary metabolites. This phase is sometimes referred to in literature as molecular farming. Products targeted for molecular farming were traditionally produced using either microorganisms or animal cell culture However, the bacterial system, while having the advantage of low cost, does not always produce the quality of protein that is required. The bacterial protein synthesis machinery does not have the means to perform post-translational modifications necessary for some protein products such as folding, glycosylation, phosphorylation, acylation and the like. On the other hand, animal cell systems are expensive and may pose dangers to human health as they could carry viruses and other pathogens.

Plants are able to perform the post-translational modifications for many proteins and unlike animal cell systems, are less expensive to grow since they utilize cheap inputs such as sunlight, soil and water. Data presented by Hood and Woodard 2002 show that plants can produce recombinant protein at a raw material cost of US$0.10 per gram. In comparison, transgenic chicken/eggs, goat's milk, and microbial fermentation cost US$2.00, US$2.00, and US$1.00, respectively. If the current standard for biomanufacturing, the Chinese Hamster Ovary (CHO), is used, the cost will be US$300 per gram. In addition, it costs more than US$250 million to put up a CHO-based biomanufacturing facility[23]. The first plant species used as a platform for recombinant protein production was tobacco since it was easy to transform and regenerate from tissue culture, but tobacco has the disadvantage of being associated with production of human toxins such as alkaloids[24]. Later studies also showed that tobacco is an expensive crop to grow and has a low protein yield[25].

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[4] Finanzen, January 31, 2006

[5] Fields of bioengineered dreams. New York Times. August 16, 2005

Plants for molecular farming can be grown the traditional way in the field. This technique has already given three commercial products: avidin, α-glucuronidase, and trypsin. Other techniques being explored are the use of hairy root cultures and cell cultures.

Hairy root culture

Plant roots have traditionally been used for various purposes other than food such as pharmaceuticals and cosmetics. Roots such as ginseng are highly valued. Extraction and purification of the active principles in roots had been a challenge to biochemists. Usually the yields are low and the active molecules could be altered by the extraction procedure. The cost of isolation and purification of proteins, for example, can be a high as 90% of total production cost[26]. Thus, it would be an advantage if the high value organic molecules can be secreted by the roots in a hydroponic medium, extracted from the liquid medium (an easier procedure than extraction from the root tissues) and subsequently purified. This process is non-destructive to the roots and the roots can continue secretion as the product is being harvested. It will result in a much higher yield of the product over time.

Plants have the natural ability to secrete substances. Phenomena such as guttation and root exudation are well known. Among various plant organs, secretion is especially well-developed in roots[27]. As much as 10% of photosynthetically fixed carbon can be secreted by roots.[28] Root exudates are known to have a natural role in plant protection and in symbiotic interactions with soil biota. Indeed there is a bewildering diversity of primary and secondary metabolites that the roots secrete to the rhizosphere. This capacity for biochemistry offers interesting possibilities for utilization if only roots can be made to grow faster so that it can produce enough quantities of secreted product to make a production system viable. This is made possible through *Agrobacterium rhizogenes*-mediated transformation, giving plants that produce an excess of "hairy roots", which can then be used intact or the roots cultured. *A. rhizogenes* acts in the same manner as *A. tumefaciens*, the workhorse of plant biotechnology. However, instead of inducing tumors, *R. rhizogenes* induces production of so-called "hairy roots". Its plasmid is therefore designated as Ri (root inducing), which contrasts with the Ti (tumor-inducing) plasmid of *A. tumefaciens*.

Plant cell culture

Regulatory approval of the world's first plant-produced recombinant vaccine was recently announced by DOW Agrosciences[2]. It is an injectible vaccine against Newcastle disease of chicken that is produced using tobacco cell cultures. This news moved plant cell culture one step ahead of organ culture (such as hairy root culture) and intact plants in the race for commercial production of recombinant vaccines using plants as a platform. While hairy root culture is still in the realm of proof of concept and scaling up problems, and intact plant culture in the field is struggling with environmental controversies[3], plant cell culture already has a

product. Yet, it will not take very long before the next approvals come, because more than 100 field trials for large-scale production of plant-derived recombinant molecules are currently awaiting approval by regulatory agencies (Joshi and Lopez 2005).

However, the DOW product is not the first commercial product derived from plant cell culture. Plant cell cultures have been used commercially to produce secondary metabolites that are produced naturally by plants. Two are in the market today: shikonin and paclitaxel (Taxol). Shikonin is an anticancer, wound-healing and anti-inflammatory, which is extracted from *Lithospermum erythrorhizon*.[29] Paclitaxel, one of the most active chemotherapeutic agents for the treatment of patients with breast cancer, is extracted from *Taxus* spp[30]. Research on plant cell culture leading to these two products became a convenient foundation on which application of recombinant DNA technology was built.

Plant cell cultures have the following advantages compared to whole plants: shorter development cycle, lower variation in yield and quality, and ease in applying good management practice (GMP).[31] It combines the ease and low cost of culture of microorganisms with the ability of higher eukaryotes (such as animal cells) to produce the quality of protein that is required in biomedical applications. Unlike animal cell cultures, plant cells do not harbor human pathogens; they also do not produce endotoxins. When the product is secreted into the culture medium, the cost of extraction and purification is much lower than that of whole plants, where downstream processing accounts for as much as 80–94% of total production costs[32]. Thus, the focus of plant cell culture R and D has been on suspension cultures which secrete the product into the medium, from which it is extracted.

b. From higher plants to other photosynthetic organisms

Successful utilization of higher plants for molecular farming has stimulated interest in exploring the simpler plants and photoautotrophs such as the mosses and algae as alternative platforms. These organisms are believed to require simpler (and cheaper) transformation and production systems and they can produce similar or better quality recombinant products. Indeed, there is an increasing intensity of research on these organisms over the last 10 years, particularly in developed countries. A cursory survey of literature in the Web of Science database gave a total of 1983 and 521 titles for the keyword algae and moss, respectively, for the year 2005. In contrast, for the keyword rice, a crop of global importance, a total of only 3793 titles came out.

The moss as a source of important genes and a platform for recombinant DNA.

The moss is hardly a plant in the traditional sense of the word. It does not have a vascular system, it does not flower and produces no seed. But it is capable of photosynthesis, hence it does not require an external carbon source. It shares many physiological and developmental traits with the higher plants. Indeed, when

its transcriptome was compared with the model plant *Arabidopsis*, more than 66% homology was found[33].

Approximately 10,000 species of mosses are known to exist[34], colonizing diverse habitats including harsh environments such as the deserts and the polar regions, where they are the most abundant plants. The *Sphagnum* peat moss can absorb up to 25 times its weight of water and are valuable commercially as nursery media and as a fuel when dry[35].

Mosses are useful to science as model systems for the study of biological processes because of their simple developmental pattern and their similarity to plants in many respects. Plant physiologists have focused on three species: *Funaria hygrometrica*, *Ceratodon purpureus* and *Physcomitrella patens*. The best studied among the mosses, *P. patens*, is a potential source of important genes for improvement of higher plants[36]. It is highly tolerant to salt, osmotic and dehydration stresses. While *A. thaliana* suffers from severe impairment of physiological functions at 100mM of NaCl, *P. patens* can grow at salt concentrations up to 600mM[37]. Plants that had lost 92% of their fresh weight during dehydration were still able to recover upon rehydration.

As a platform for recombinant DNA expression, the moss combines the advantages of microorganisms and higher plants. Like bacteria and yeasts, it integrates foreign genes mainly by homologous recombination[38]. It is unique among plants in this capability. This creates the possibility of targeted integration of foreign DNA which is very useful not only for the study of gene function but also for genetic engineering. This advantage is further enhanced by the fact that the gametophytic phase dominates its life cycle and it is self-fertile.

Its haploid tissue can be propagated vegetatively[39]. Cultivation of the juvenile protonemal stage in a bioreactor system makes it possible to easily recover secreted metabolites and avoid regulatory hurdles that are now facing transgenic higher plants. Taken together, the moss bioreactor system can produce products of recombinant DNA cheaper than higher plants. Its main disadvantage compared to microorganisms is its relatively slow growth rate.

Algae as a platform for recombinant DNA

Like plants, algae are capable of photosynthesis. In fact, algae are responsible for about half of the total photosynthesis on earth![40] Algae thrive in diverse aquatic environments, such as the sea, freshwater, in hot springs and even in highly polluted water. They are used as food, fertilizers, animal feed, biofuel, as an agent for bioremediation, and a source of high value products such as pigments, cosmetics and food supplements. Algae are a highly diverse group of organisms – some are related to bacteria, but others are closer to higher plants. They are relatively unexplored. Approximately 36,000 known species represent only 17% of the total number of species that actually exist[41]. Of these, only very few are used in industrial scale.

There are two classes of algae: the macroalgae and microalgae. Between the two, the latter is the favored object of genetic engineering research. The popular species of microalgae include *Chlorella*, *Spirulina* and *Dunaliella*. Aggregately at present, microalgae are economically less important than macroalgae which include seaweeds. Microalgae are used as whole cells or for extraction of cellular products such as β-carotene, phycobiliproteins, astaxanthin and polyunsaturated fatty acids (PUFA). β-carotene extracted from *Dunaliella salina* grown in saline ponds represent more than 80% of the world's supply of natural β-carotene.[42] The main constraint to increased utilization of microalgae for industrial scale production of cellular products is the high production cost. Therefore, there is great research interest in overexpression of desired molecules from endogenous genes or expression of heterologous genes.

As a platform for expression of recombinant proteins, microalgae have the advantage of shorter production time, lower production and scale up costs compared to higher plants[43]. Species such as *Dunaliella* and *Chlorella* grow in saline waters, thus their large scale culture does not compete with conventional agriculture for the use of land and water. In the case of bioreactor systems, the requirements are simple since many algae are photoautotrophs. It is possible to develop culture systems that utilize secretory mechanisms through genetic engineering so that the recombinant proteins can be released directly into the culture medium, where these can be extracted with relative ease.

Making Agricultural Biotechnology Work for the Philippines
Translating Policy into Programs

So far, agricultural biotechnology has enjoyed good support from various sectors of Philippine society. These include a highly supportive government, industry and science community. Particularly encouraging is the recent report of a survey[44], which involved middle class youth (average age is 20 years), the future leaders of this country. The survey showed that 80% of the respondents were interested to highly interested in science and technology, and 82% believed that biotechnology will improve their lives. Surprisingly, pest resistant crops were among the products of biotechnology that obtained the highest approval ratings (78%). These are the products, specifically Bt corn, that had the most negative publicity because these are the first products to be released for local cultivation. The Philippines can build on this reservoir of goodwill to develop a program that will not only generate support for biotech products that are being exported to this country, as current short term efforts tend to achieve, but also one that will make biotechnology a creator of local jobs and wealth. A 2004 series of case studies on health biotechnology[45] enumerates the ingredients needed to create successful innovations in biotechnology. We highlight some of the recommendations below.

Political will. This means more than passing a law or formulating a set of guidelines supporting biotechnology; we already have these. It also means policy

coherence; we cannot have the Department of Agriculture and the Department of Science and Technology saying yes to biotechnology and the Department of Environment, and various local government units saying no. We cannot have a government saying that biotechnology should move forward, and the same government putting the brakes by imposing stricter regulations that are justified more by politics than science. It also means giving priority to biotech R and D in the national budget as Vietnam has done. It also means responding to the brain drain by creating incentives for scientists not to leave and for those who have left to return as China has done. One such incentive is salary and the prestige that goes with it. Something has to be done about the current situation where knowledge-oriented professions are in the bottom quarter of the salary ladder.

Individual leadership. Historically, leadership is a key element in every field of human endeavor. The leader provides the vision, the direction, and inspiration. This is true for Singapore, whose Deputy Prime Minister Dr. Go Keng Swee dreamed of establishing an institution that is equivalent to the Weizmann Institute of Israel, a state-funded center for scientific excellence. Professors in Malaysia take pride in recalling that one of the first acts that the former Prime Minister Mahathir did when he was new in the office was to elevate the privileges of Professors to the level of Ministers.

Close linkages. This may seem odd for the field of science and technology. People on the streets associate great discoveries with the heroic efforts or genius of one man such as Darwin, Newton, Galileo and Einstein. But these are exceptions rather than the rule. In recent years, great discoveries are products of coordinated work among tens if not hundreds of geniuses. In the field of physics, one is reminded of the Manhattan project in the 1940s that led to the production of the world's first atomic bomb. In the field of biology, one is reminded of the Human Genome Project, which involved five major and fifteen smaller centers in five countries representing three continents[46]. The birth of the science of molecular biology is a product of collaboration between an American (James Watson, a biologist) and an Englishman (Francis Crick, a physicist).

Collaboration among scientists can be done at many levels. It may be as simple as collaboration between two individuals working in the same laboratory or the same department. Or it may extend to collaboration among research institutes crossing national borders. The value of collaboration is repeatedly illustrated in recent literature. Indeed, the 2001 UNDP report on Technology and Development emphasized the need for collaboration. Inspired by the double helix of DNA, the UNDP report proposed a triple helix model of collaboration among academe, industry and government.

To assist researchers in negotiating scientific collaborations, a set of guidelines was proposed by Smalheiser et al 2005[47]. Covered by the guidelines are seven major concerns: 1) sharing of reagents and data, 2) design of experiments, 3) division of labor, 4) publication of results, 5) co-authorship order, 6) access to unpublished data and 7) intellectual property issues.

Enterprise creation. Collaboration between government and the academe in the field of biotechnology is fairly well established in the Philippines. This is partly because of a very strong presence of former university professors in various government departments, either in advisory capacity or as part of the bureaucracy. But this kind of collaboration is not enough to bring the products of research to the consumers. At best, this kind of collaboration will produce 'proofs of concept' that can be published in prestigious journals or earn best paper awards in scientific conferences. Indeed, out of thousands of public sector research projects on plant biotechnology worldwide, there are only two successful transgenic crops that were developed through public sector efforts[48]. What seems to be the missing ingredient? The study by Thorsteinsdottir (2004) sums it up: "private firms were essential for integrating various sources of knowledge in health biotechnology and turning them into products and services".

Delmer 2005 describes the predicament of the public sector: " There are plenty of public-sector scientists who can create transgenic plants in their laboratories. What has been sadly lacking in the public sector is an understanding of how to make strategic assessments of which projects can have the highest impact; how to choose the best varieties for transformation and to design the best constructs to ensure the freedom to operate and gain regulatory approval; the recognition of the need to generate very large numbers of transformants to ensure high levels of expression and the stability of the inserts and to determine the optimal promoter; and a clear plan for the stewardship, uptake, and dissemination of new varieties."

The failure by government and academe to bring products of research to the consumer is not for lack of trying. Recent history in the Philippines is full of heroic efforts by the academe and government working independently or together to bring products of public sector research to the farmers' field. This includes such products as improved varieties of crops, biofertilizers, and biopesticides. The government spent a lot of money training government technicians and putting up seed farms and production laboratories such as insect rearing houses and tissue culture facilities. Many of these did not last very long. When subsidy ran out so did the projects. In many cases, the products were simply not marketable to begin with.

How can the government and academe work with private industry to bring products of biotechnology to the consumers? In developed countries, this is simpler, because private industry exists. In the developing world, it is much more complex, because in many cases, private industry dedicated to biotechnology does not even exist.

There are many models of government- or academe-initiated enterprise creation. Thorsteinsdottir (2004) described some of these. South Korea allows university professors to set up private firms or spin-off companies. China, converted some existing research institutions into companies that manufacture medicine. Favorable policies are essential for private sector participation.

But favorable policy apparently is not sufficient[49]. Private funding is an elusive factor for success. Without money from investors who have faith and experience in the biotech business, it is impossible to support the biotech industry considering the cost not only of R and D but also of complying with regulations, use of intellectual property and neutralizing negative publicity. In India, venture capital is emerging from various sources, including state governments, insurance companies and banking institutions. These, in turn, help encourage foreign investors. In the Philippines, there is really no shortage of capital but what is lacking is the faith in the business prospects of biotechnology; this, at the present time, needs to be imported, in the same manner that we had to import faith in the business prospects of a seed industry in the 1980s.

Intellectual property. The industrial revolution, the predecessor of the current bioindustry revolution, started in Europe in the beginning of the modern era because it was in Europe where intellectual property was first recognized and protected by law through patents and other forms of legal protection. Innovation was promoted by this policy. Developing countries in Asia that were able to develop domestic industries initially favored lenient patent legislation that allowed them to "reverse engineer" existing technologies. Otherwise, they waited for patents to expire and then they manufactured generic products. This is best illustrated in recent years by generic drugs and agricultural chemicals. But today, these approaches are no longer tenable because of the strengthening global intellectual property regime and the diversity of means for enforcement. In addition, the rapid turnover of technology creates a highly competitive field, where technology serves as the competitive edge. By the time patents expire, the technology would be obsolete. This was true in the computer industry; this is clearly true also for bioindustry. The recognition of this trend has convinced many poor countries to invest heavily on R and D on biotechnology.

The heavy public sector investment in biotechnology now serves as a powerful motivation for developing country governments to strengthen their intellectual property regimes. After all, they need to protect their own technologies from piracy. But even without a sizeable government investment in R and D, the need for an effective intellectual property regime is dictated by the need for private investment.

The real challenge is not how to creatively avoid IP regimes but how to creatively operate within the IP environment. Facing this challenge has been the expertise of private industry that has to deal with IP issues almost on a day to day basis. Unfortunately, to most public R and D institutions IP is an unfamiliar ground.

There are basically two levels of IP concern for the public R and D institutions: how to access privately developed technology for R and D use, and how to bring publicly developed technologies to the consumers via the private sector. There are no clear answers to questions associated with both concerns. However, there are models already in operation[50]. On one hand, access to private sector technologies is being facilitated by such organization as the African Agricultural Technology Foundation, which was established to negotiate access to private sector

technologies and assist with stewardship issues. A local example is the recent signing of a license agreement among the Maharasthra Hybrid Seed Company (MAHYCO), a technology donor, the Sathguru Management Consultants Private Limited, as technology facilitator, and the University of the Philippines in Los Banos (UPLB), as technology user. Under this agreement, UPLB will use Bt eggplant parental lines of MAHYCO in a backcross program with elite Philippine eggplant varieties. On the other hand, access to public sector technologies are being facilitated by new models of licensing such as that being developed by the Public Intellectual Property Resource for Agriculture (PIPRA) and by the Biological Innovation for an Open Society (BIOS). Under the open-source licensing promoted by this program, users of technology have free access to technology on condition that improvements that result from this use are placed in the public domain.

Improving literacy in biotechnology

The generally low level of public understanding of the science behind genetic engineering possibly contributes to negative perception and rejection of its products. In a 2002 street interviews in Metro Manila, Jakarta, Beijing, Shanghai and Guangzhou, respondents were asked if they had eaten DNA. Only two of five people gave the correct answer[51]. Only one in three correctly recognized as false the statement "Ordinary soybeans do not contain genes while genetically modified ones do."

Indicators of local public support for science in general are not very positive. The Department of Science and Technology, the national government's arm for R and D and promotion of science has one of the lowest budgets among the major units of the government. College enrollment in natural science programs in 2000-2001 was only 0.89% of the total college population[52]. Salaries of scientists and researchers are in bottom quarter of the list of occupations.[53]

A public that has a low regard for science and does not value innovation is an easy prey for critics of biotechnology who portray the product as a hazardous piece of junk being shoved into their throat by profit hungry businessmen. In the final analysis, this is the root of the controversies regarding biotechnology in this country. If one combines negative public attitude with excessive regulation, the result is a very bleak future for biotechnology. Biotechnology will be selling an expensive product that nobody wants.

The effects of low public appreciation for science and technology include susceptibility to negative propaganda, consumer rejection and excessively restrictive regulations not only of scientific research, but also of technological applications. This cause-and-effect relationship could make a vicious cycle that result in further reduction of scientific literacy and even more restrictive regulations. To break this cycle, the logical approach is to improve scientific literacy.

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Among many fields of science, those associated with biotechnology are most susceptible to misunderstanding today partly because of the negative publicity that has been sustained globally and locally for almost 10 years now. The interested sector of the public has been polarized into those who strongly oppose and those who strongly support biotechnology. Lack of scientific understanding compromises the quality of debates, and argumentation invariably leads to political and ideological domains, which are even more complicated than science itself. Issues become muddled and the outcome could range from extremes to the "safer" no-decision type of decision as postponement (moratorium) or let-the-public decide type of decision as labeling. Yet, these "safe" decisions are not "safe" at all. Even labeling, which sounds so neutral, can cause confusion contrary to what it purports to do, as well as increase the cost of biotech products relative to conventional counterparts[54]. If biotechnology is truly beneficial, as advocates contend, then even the "safe" decisions could deprive the public by default of an important solution to their problems. Thus, any decision about biotechnology carries a risk, which is best assessed on the background of knowledge.

On another vein, literacy on biotechnology is essential today as its impact is so intimate. It is in the food we eat, in human health and integrity of the environment. No technology is more intimately connected to our day-to-day existence.

There are existing global and local programs for public education on biotechnology. These range from industry-supported, which are strongly pro-biotechnology; to those that are supported by known anti-biotech advocates such as Friends of the Earth and Greenpeace. Branches of the Philippine government, such as the Department of Agriculture and the Department of Science and Technology, had been engaged in public information activities which involve multi-media as well as face-to-face seminars since the introduction of the first GM crop (Bt corn) in the Pbilippines in 2002. The main limitation of these public information activities is that they lack the depth of treatment that is needed for understanding of biotechnology. Typically, the message is so simplified that it creates misunderstanding. For example, powerful images such as Frankenstein-type monsters are being fed to the public imagination by anti-biotech campaigners. Advocates, on the other hand, are tempted to present exaggerated estimates of benefits, extrapolating limited research data, to generate sympathy. Another serious limitation of the current public information approach is that they have very limited reach. In many seminars, for example, it is usual to see the same faces —those who have already made up their mind to oppose or support biotechnology. They attend the seminar not to learn but to push their preconceived ideas; otherwise, to show their support for the organizers of the seminar or amuse themselves with the theatrics of seminar speakers. But the most serious limitation is that current campaigns are fund-driven, and therefore, short-term in nature. At its best, the motives of campaigners are suspect, as they could be perceived as mercenaries working for interest groups. Indeed, in some public debates, opposing camps so successfully picture their opponents as paid lackeys that they end up both discredited in a contest where everyone loses, including the audience.

There is a need for a more sustained, in-depth, far-reaching, and credible public education. This is the key to responsible decisions about biotechnology. The logical venue for this type of education is the classroom—— formal education. Unfortunately, classroom coverage of biotechnology is very limited at present. Interest in classroom coverage of biotechnology can be traced to the first Biotechnology Education Council meeting in the University of Iowa in the USA in 1994, which was convened to help teachers integrate biotechnology in various school curricula[55]. During that meeting, three major hurdles were recognized: 1) educators lacked the content and technical knowledge to feel comfortable about integrating biotechnology in their curricula; 2) there was a serious shortage of money for supplies, equipment and release time for educators to obtain training; and 3) there was little time during the day and in classrooms to prepare and present biotechnology. Since then, the hurdles have been progressively eliminated. Today, there are many internet sites[4] offering free course resources such as course outlines, laboratory manuals, movie clips, graphics and even powerpoint presentations. The initial problem of lack of textbooks in biotechnology has been addressed with publications by such authors as Watson[56], Micklos[57], and Glick[58] in North America and Slater[59] in the United Kingdom. A series of methods oriented books was also published by the Humana Press[60], CRC Press[61] and Oxford University Press[62] among others. E-mail groups of instructors share ideas as well as laboratory techniques. For Science and Society type of courses, books written by scientists include Mendel in the Kitchen by Fedoroff and Brown[63], Biotechnology and Safety Assessment by Thomas and Fuchs[64] and Genetically Modified Planet by Stewart[65]. A number of books written in popular style was written by journalists. Among them is the Biotech Century written by Rifkins[66], which has served as the inspiration of the anti-biotech movement. The Genomics Age written by Smith[67], More than Human by Naam[68] and Genome by Ridley[69] are well received by readers.

In the Philippines, a systematic effort to encourage integration of biotechnology in the undergraduate curricula of state universities nationwide was initiated by the author in 2005. Activities include workshops on biotech course proposal preparation, as well as sharing of teaching resources and experience. Filipino teachers are faced with similar constraints that educators in the USA faced in the early 1990s. But unlike American teachers who have to develop materials from scratch, Filipinos have the advantage of access to many of the resources developed by their American counterpart. What is lacking today is active support from university administrations to develop biotech oriented courses and provide funding for training of teachers, development of libraries and laboratories. It is not as simple as adding one or two courses, because biotechnology covers a broad range of human thought. Its science is rooted in biochemistry, computer science, microbiology among others. Its politics and business is rooted in philosophy, ethics, economics, and religion among others. Full integration of biotechnology in the school curricula may mean no less than an overhaul of the curriculum, a task

that will require contributions from Professors, university administrators and the Commission on Higher Education.

We need to rationalize biotech regulations

The Philippines has a good history of making rules and regulations even before there is something to regulate. Call that anticipation, or maybe it is simply easier to make rules than play the game. This is true for biotechnology. The Philippines was well ahead of its neighbors in creating a National Committee on Biosafety in October 1990 through Executive Order 430[70]. The Executive Order prescribed regulation for contained work, large scale contained work and glasshouse trials, and guidelines for single-site field trials. Subsequently in April 2002, the Department of Agriculture issued Administrative Order No. 8, which prescribed the guidelines for commercialization of biotech plant and plant products. This was followed by Memorandum Circular No. 8, effective July 1, 2003, which prescribed the requirements for importation of biotech products. Memorandum Circulars No. 11 and 12 issued in August 2003, further clarified the import rules for biotech products for direct use as seed, food, feed or for further processing.

On the positive side, it is precisely because we have rules that it had been possible to approve biotech activities and products. Other Asian countries did not have the luxury of having rules until recently. This is the reason why the Philippines has the distinction of being the only Asian country that has approved a GM food/feed crop (maize) for commercial cultivation. As of July 2005, the Philippines has approved 19 transformation events for use as food, feed, processing or propagation. Of these, three are approved for propagation. In addition, the country has approved seven stacked trait products for importation for direct use as food and feed.

The bad news is that the regulatory regime of the Philippines for transgenic crops has been considered very strict by international standards. ADB 2001 described the approval guidelines in the following manner:

"The present set of biosafety guidelines is one of the strictest in the world. The guidelines were originally patterned after those first used in Australia, Japan and US during the early 1980s. Since then, all these countries have relaxed most of their guidelines as a result of new technical data and familiarity in dealing with new products. The Philippines, however, has not relaxed its guidelines."

On the contrary, our guidelines have become more strict, as we started to implement the Cartagena protocol even before we have actually ratified it. That is a record by itself! The National Biosafety Framework (NBF), which was recently approved as the new standard for GM crop evaluation is proudly described by its authors as "going beyond the Cartagena protocol". It makes socio-economic, cultural and ethical considerations a requirement for developing biosafety policies[71]. It also mandates "consensus building" and adherence to the principle of subsidiarity, meaning that all levels of government, including the local government units shall participate in implementing the biosafety framework. In short, the approval process becomes a political exercise rather than a biosafety evaluation,

which incidentally, is what the Cartagena protocol is all about, which explains why it is called the Cartagena Protocol on Biosafety in the first place. Environmental impact assessment (EIA) is also mentioned presumably as an option that regulators may impose under guidelines yet to be formulated. (The EIA is a process that has been previously imposed only on "environmentally critical projects" such as nuclear power plants). What this means is that the cost of securing approval for GMOs will likely become prohibitive, and only large multinational companies can afford it. Considering that the current biosafety rules are already too expensive, approval of the NBF will effectively prevent the products of local R and D and that of small companies, from reaching farmers. Thus, we can look forward to a biotech future that is dominated by few large multinational companies[72], which is precisely what many critics of biotechnology are trying to avoid when they pushed for strict regulation.

Regulations are formulated for various reasons: ideological, political, religious, social, economic. What we have is a product of all of these, perhaps some prevailing over others. Since I am not an expert on any of these, let me focus on the scientific basis of regulations.

The latest revisions in the procedure for approval of genetically modified crops is based on the Cartagena Protocol on Biosafety, an international agreement that was negotiated during the period 1992 to 2000. The most important assumption that guided the drafting of this protocol is that GM crops are in the same category as nuclear power plants and toxic wastes. This was probably a reasonable assumption in the beginning, when the world has not seen a single GM crop in the field, and we knew very little about the consequences of genetic modification.

Since then, the world has grown more than one billion acres of genetically modified crops in a wide range of environments over a period of 10 years. In addition, hundreds of studies have been completed on the issue of safety of genetically modified crops. The results clearly challenge the validity of the Protocol's assumption. Among the most important reviews of the relevant studies are the following:

1. A GM Science Review commissioned by the UK government and documented in two volumes of reports which were published in 2003 and 2004[73]. The highlights of the reports are:
   a. For human health, to date there is no evidence that currently commercialized GM crop varieties or foods made from them are toxic, allergenic, or nutritionally deleterious.
   b. Transgenic DNA and non-transgenic DNA appear, from studies conducted, to share the same fate once ingested by humans, being very largely, but not entirely, degraded in the gut. There is no compelling evidence of gene transfer from food to bacteria in the human gut. Several research studies have been unable to find transgenic DNA (or its gene products) in milk, meat or eggs produced from animals fed on GM crops.

c. Detailed field experiments on several GM crops, in a range of environments have demonstrated that they are very unlikely to invade our countryside or become problematic plants, nor are they likely to be toxic to wildlife or to perturb soil structure in such a way that the functioning of soil communities is substantially affected.
d. Field studies indicate that there is very little gene flow from transgenic crops to wild relatives.
e. The few studies that have been carried out so far have been unable to detect evidence for horizontal gene flow between GM plants and either bacteria in the soil or viruses.
f. To date, in countries that have the experience of growing GM crops, there have been no reports of their causing any significant environmental damage.

2. A study conducted by the World Health Organization, the results of which were released in 2005[74] . The report concluded that GM foods currently available in the international market have undergone risk assessments and are not likely to present risks for human health in any other form than their conventional counterpart.

3. A study on the adequacy of USA regulation of GM crops, conducted by the National Academy of Sciences[75]. The highlights follow:
   a. It is generally assumed that the risk associated with the introduction of genetic novelty is related to the number of genetic changes and the origin of the novel genes. The committee found no general support for this assumption. A priori there is no strict dichotomy between the possibility of environmental hazard associated with releases of cultivated plants with novel traits and introduction of nonindigenous plant species. However, the highly domesticated characteristics of many cultivated plants decrease the potential of certain hazards.
   b. Both transgenic and conventional approaches for adding genetic variation to crops can cause changes in the plant genome that result in unintended effects on crop traits. A comparison of unintended effects caused by various breeding methods is presented in NAS (2004).[76]
   c. The committee finds that the transgenic process presents no new categories of risk compared to conventional methods of crop improvement but that specific traits introduced by both approaches can pose unique risks.

4. A study on the global socio-economic impact of GM crops, published in 2005[77]. Highlights of the results follow:
   a. There has been about a 14% net reduction in the environmental footprint on the cropping area devoted to GM crops since 1996. The total volume of active ingredients applied to crops has also fallen by 6%.

b. Reduced fuel use from less frequent herbicide or insecticide applications and a reduction in the energy use in soil cultivation. In 2004, about 1,082 million kg reduction of carbon dioxide emissions arising from reduced fuel use of 400 million liters.
c. In North and South America, 2,568 million kg of soil carbon sequestered in 2004.
d. The combined GM crop-related carbon dioxide emission savings from reduced fuel use and additional carbon sequestration in 2004 were equivalent to the removal from the roads of nearly 4.7 million cars.

5. A report of the National Academy of Sciences (USA) on the safety of genetically modified foods, published in 2004[78]. Highlight: The policy to assess products based exclusively on their method of breeding is scientifically unjustified.

In addition to challenging the fundamental assumption of the Cartagena protocol, the above studies clearly show that the current distinction in the Philippines between GM and non-GM as far as regulation has a shaky scientific basis. On the basis of our long experience with plant breeding, experience with biotechnology crops, new knowledge from genomics, and new knowledge about the consequences of transgenesis at the genomic level as presented in this paper, we can support a proposal made last year by a group of authors from different universities in the USA[79]. The principle behind this proposal is stated as: "if a gene or trait is safe, the genetic engineering process itself presents little potential for unexpected consequences that would not be identified or eliminated in the variety development process before commercialization". We have a long history of the safe use of novel varieties using an array of methods, many of which are more disruptive of genomes than genetic engineering. The safe use had been based on an approval process that is based on evaluation of the phenotypes or traits rather than on the process that gave the phenotype.

We quote some of the salient features of the proposal:

1. Some genes presently assumed to be unsafe by the regulatory process should be exempt:
   - *Agrobacterium* DNA. This bacterium transfers DNA naturally to plant genomes. Some plants, notably tobacco, have native genes that are originally from *Agrobacterium rhizogenes*.
   - Plant viral DNA, specifically those used as promoters or terminators, or used to suppress other viral DNA, such as those used in PRSV resistant papaya. These sequences, by themselves, do not pose any hazard. We have been consuming viral sequences in the food we eat long before genetic engineering.
   - Well-known markers that impart antibiotic resistance. During the deregulation process of Flavr Savr tomato, the product of *nptII* gene has

been classified as general recognized as safe (GRAS). Other studies supported this position.

- Selected marker genes that impart reporter phenotypes, such as â-glucuronidase reporter gene and the green fluorescent protein. There are strong evidences supporting the safety of these genes from the point of view of human health and environmental safety.

2. Create regulatory classes in proportion to potential risk.
   - Low risk – where the imparted traits are functionally equivalent to those manipulated in conventional breeding and where no novel biochemical or enzymatic functions are imparted, such as "domesticating genes" (sterility, dwarfism, seed retention, modified lignin).
   - Moderate risk – plant-made pharmaceuticals and industrial proteins, plants with novel products that have very low human and environmental toxicity, or that are grown in non-food crops and low nontarget ecological effects.
   - High risk – careful regulation of plants producing plant-made pharmaceuticals/industrial proteins is needed during field testing and commercial production where transgene products have a documented likelihood to cause significant harm to humans or environment.

3. Eliminate event-specific basis of transgenic regulation. The assumption of this rule is that the uncertainties associated with transgenesis exceed those of conventional breeding methods such as wide crosses and mutagenesis and they create safety concerns that are not adequately addressed during subsequent steps in variety development. This assumption is not supported by our experience with mutagenesis, a more disruptive procedure than transgenesis, which has produced more than 2000 commercial varieties.

   Another assumption is that the location of a transgene can significantly influence its function or that of endogenous genes. This is not supported by new knowledge about genomes, which shows that genomes are highly dynamic. Total DNA content, the number of genes, and gene order can vary significantly among varieties of the same species. Significant differences in colinearity occur among varieties while retaining phenotypic functions. Transposable elements routinely move into and out of genes, where they can alter gene expression or site of chromosome breakage or rearrangement. It is futile to attempt to define a standard genome for a species or even a variety against which to compare changes due to transgene insertion.

   The use of event-specific regulation has adverse consequences, among which is the use of the same event over and over in a backcross program, rather than direct transformation of elite varieties. This reduces the response time in making useful varieties for farmers and increases the cost of variety creation. For crops that have long life cycles such as fruit trees, the backcrossing approach is practically impossible.

   Lastly, event-specific regulation unnecessarily increases the cost of obtaining regulatory approval.

Summary

The world is ripe for a third agricultural revolution, which is more challenging than the first, the beginning of agriculture itself, and the second, the Green Revolution, because of the limitations in natural resources that we face today. Technology, specifically genetic engineering among others, will be needed to overcome these constraints. Agricultural biotechnology will be needed to provide a growing population not only with the traditional products of agriculture (food, feed and fiber), but also energy, fuels, materials and drugs.

Current concerns about the predictability and safety of plant biotechnology are being addressed by new technologies such as molecular profiling that allow a more comprehensive analysis of the consequences of transgenesis. New technologies such as selectable markers and promoters of plant origin, plastid transformation, cell and organ cultures provide an assurance of safety. There is a clear shift in interest from higher to lower plants such as mosses and algae, as platforms for production of high value industrial and biopharmaceutical products.

To make the third agricultural revolution happen in the Philippines, the paper enumerated three requirements. The first is translating favorable policy into programs. This will require political will, leadership, close linkages, enterprise creation, and ability to function even in the regime of intellectual property rights. The second is improving literacy in biotechnology in order to break the vicious cycle of low literacy, restrictive policies and consumer rejection. The author argued for integration of biotechnology in formal education curricula as a sustainable approach to literacy enhancement. Lastly, the author proposed a rationalization of biotech regulations, observing that the fundamental assumptions regarding safety of GM crops that provided the basis for existing regulations are no longer tenable considering the body of scientific knowledge generated during the first 10 years of GM crop commercialization.

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