Accelerating the commercialization of home-grown genetically engineered crops

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Transgenic crops offer the state-of-the-art, and yet simple-to-use technologies for sustainable enhancement of agricultural productivity. During the last 20 years, several research groups in India have developed capabilities in genetic engineering of crop plant species and some of them have isolated promising genes and promoters, with potential for commercialization. However, isolated growth of researchers, limited R&D infrastructure and knowledge base available in the seed industry, and the regulatory processes involved in the release of transgenic cultivars pose serious challenges to accelerating the conversion of such leads into field crops. There is an urgent need to evolve efficient managerial approaches for developing and advancing genetically engineered cultivars into Indian agriculture. This article emphasizes the need to identify the most promising transgenics and genes available in the country, evaluate the related intellectual property issues and provide unstinted support to accelerate the process of their commercialization. An approach that would synergize public–public and public–private partnerships needs to be evolved. Initially, it may be driven by public sector through crop- and trait-specific consortia, comprising researchers and the seed industry. A few of such examples should be taken to the stage of clearance by GEAC for unregulated release of indigenously developed transgenic cultivars. These would then serve as role models and catalyse the formation of need-based teams and lasting partnerships, needed to usher Indian agriculture into a globally competitive phase of sustainable productivity.

IT has been amply demonstrated that genetically engineered (GE) seeds, developed using recombinant-DNA techniques (also referred to as transgenics, or genetically modified organisms (GMOs)), provide an easily adaptable, scale-neutral technology for the farmers. Even farmers with small land holdings can benefit from the high technology when such seeds become available to them at reasonable cost. Changes required in the existing crop management practices, or additional inputs are minimal. The Task Force on Agricultural Biotechnology constituted recently by the Ministry of Agriculture recommended[1] that 'High priority should be accorded in transgenic approach to the incorporation of resistance to insect-pests and diseases, including viruses and to drought and salinity (i.e. biotic and abiotic stresses)'. Genetic engineering provides great opportunities to enhance crop productivity, reduce the amount of pesticides applied in the field, and bring down the cost of production. Many laboratories in the country have been engaged in GE of crop plants for several years[2]. However, the progress in commercializing the indigenously developed GE crops has been slow. Even globally, only two traits – herbicide and insect resistance have been deployed extensively in the development of transgenic cultivars. This point was also made by Pental[3]: 'How is it that while in the laboratories a large number of transgenics have been developed – very few are in the field?' This article addresses the issue of converting laboratory demonstrations of GE crop plants into marketable cultivars and hybrids for large-scale cultivation in India, and suggests measures to expedite this process.

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The global and Indian scene

Globally, transgenic crops were grown during 2003 on nearly 70 mha of land[4]. In contrast, the coverage in India was less than 100,000 ha compared to 2.8 mha in China. The first, and as yet, the only GE crop permitted for commercial cultivation in India is cotton that expresses a **d**-endotoxin gene (c*ry1Ac*) from *Bacillus thuringiensis* for bollworm resistance, popularly known as *Bt*-cotton. Three hybrids with the *Bt* gene were approved for planting by the farmers in 2002. These were developed by the Maharashtra Hybrid Seeds Company (MAHYCO), using the technology licensed from Monsanto Co, St. Louis. Convinced by the overall performance of *Bt*-cotton, several other smaller seed companies have now entered into licensing arrangements with Monsanto for the same gene, in spite of the high cost of technology transfer. This illustrates that even small seed companies are willing to invest funds when they are convinced about the advantage and expected returns. Precedence of bio-safety approval from the regulatory authority (GEAC) for the gene, makes them comfortable with their investment decision in this case.

At the same time, opposition in many parts of the world, including India, against the cultivation of GE crops has hindered their commercialization. Indian opposition is not as much against GE technology, but is primed by fears related to possible dependence of Indian seed companies on imported technologies from multinational corporations (MNCs). There are widespread apprehensions in India even among senior agricultural scientists that the high technology seeds in the hands of MNCs, in future, may make the Indian farmers largely dependent on them for their seed requirements. The authors believe that competition between imported and indigenously developed technologies can provide a wider choice of seeds to the farmers at equitable costs. Pharmaceutical industry in the country is a good example of growth catalysed by such competition. Generic drugs from multiple, local manufacturers have been helpful in keeping a check on the prices charged to the consumers. In recent years, public and private sector networking has also led to the identification of new drug molecules. Some of the private players in the pharma industry are poised to become MNCs of Indian origin. Availability of proprietary (private) as well as public-bred hybrid seeds in the past few years in India indicates that, farmers benefit from wider options, and select the hybrids that give them higher economic returns. Continual improvements are made by the seed producers to enhance their market share. The authors believe that in the high-technology areas of GE seeds, there is need for the public-funded research laboratories to establish complementing partnerships with the private seed industry. This alone can ensure expedient development, and adequate availability of quality seeds packaged with the state-of-the-art technologies, matching the global advances made by MNCs.

The organized seed market in India is less than 3% of the global market, which is estimated at about US$ 30 billion. The purchased seed covers only 10% of the total area planted[5] in the country, the rest is sown either with the seed saved at the farm or obtained from neighbouring farmers. This huge gap needs to be reduced by enhancing awareness of, and supplying quality seeds. In the absence of variety protection, private seed companies largely restrict themselves to the selling of hybrids where the parental stocks remain with the company. The same would be true for the GE seeds; private seed companies would prefer selling mainly the hybrids, where new seed needs to be bought each year from the company. The seed saved from the harvest, if used for planting, gives lower productivity due to segregation. In this respect, public sector institutes need to play the benevolent role of developing GE cultivars in crops where hybrids are not feasible. Heterotic breeding should be preferred for crops where the increased productivity compensates for the higher cost of hybrid seed. This would further promote initiatives from private seed companies. The Chinese approach to *Bt*-cotton is worth mentioning in this context. China licensed cultivation of imported Bollgard *Bt*-cotton developed by Monsanto in 1997, which was rapidly accepted[6]. At the same time, indigenously developed hybrid cotton with locally isolated *Bt* genes was also introduced in 1998. In 2002, Bollgard and locally developed *Bt*-hybrids respectively, covered 55 and 45% of the total *Bt*-cotton area. Thus the Chinese Academy of Agricultural Sciences has already set up an example by evolving an alternative to *Bt*-cotton from Monsanto. India can also open new opportunities by executing a carefully planned strategy to meet national needs.

The local successes

Excellent leads obtained in genetic enhancement of crop plants, using the R-DNA techniques in several laboratories supported by public funds in the country, have been listed by Sharma *et al.*[7]. During the last few years, among others, research laboratories at the Indian Agricultural Research Institute, National Botanical Research Institute (NBRI), Delhi University (South Campus), International Centre for Genetic Engineering and Biotechnology, National Centre for Plant Genomic Research, Tamil Nadu Agriculture University, Osmania University, International Crop Research Institute for Semi-Arid Tropics, etc. have spent substantial efforts towards the development of transgenic crop plants improved for resistance to insect pests, disease, drought and salinity stress, higher protein content, and male sterility for hybrid seed production. The cases where satisfactory expression levels have been reported in agricultural crops are listed in Table 1.

Novel genes and promoters developed at NBRI

Novel genes[8], promoters[9] and other related technologies[10] useful for the development of GE crops have been developed at NBRI, Lucknow. A synthetic gene[8] that codes for a chimeric protein designed for high level of toxicity to an insect, *Spodoptera litura* has been designed. This herbivore damages a number of crop species, including cotton, groundnut, castor and vegetable crops. The novel gene has been patented and used for developing transgenic cotton and groundnut. A second gene (modified *cry1Ac*) that targets another major pest of cotton (*Helicoverpa armigera*) has also been designed and synthesized at NBRI. The two transgenic *Bt*-cotton lines show a high level of resistance to bollworms in laboratory tests. These *Bt*-cotton lines have recently been licensed to Swarnabharat Biotechnics Pvt Ltd, Hyderabad, which is a consortium of seven reputed Indian seed companies. The contributions of NBRI to the development of indigenous *Bt*-cotton and catalysing partnership among several seed companies have received wide attention

Table 1. Significant reports on agriculturally useful transgenic crop plants developed in Indian laboratories

Crop	Trait	Reference
Cotton	Transgenics expressing novel *cry1EC* and *cry1Ac* genes for resistance to bollworms *Spodoptera litura* and *Helicoverpa armigera*	8
Brassica juncea (Indian mustard)	Transgenic male sterile (*barnase*)/restorer (*barstar*) lines for heterotic breeding	21
Indica rice	Transgenics expressing snowdrop lectin gene for resistance to sap sucking insects, brown planthopper and green leafhopper	22
Indica rice	Transgenics expressing *cry1Ac* for resistance to stem borer	23
Indica rice	Transgenics expressing *cry1Ac* for resistance to yellow stem borer	24
Potato	Transgenics expressing *Amaranthus* seed albumin for nutritional enhancement	25
Solanum melongena (brinjal), tomato	Transgenics expressing *cry1Ac* for resistance to fruit borers	26, 27
Banana	Transgenics expressing magainin analogue for enhanced disease resistance	28
Brinjal	Transgenics expressing mannitol phosphodehydrogenase for abiotic stress tolerance	29

internationally[11] and nationally[12]. Many other Indian seed companies and state-level organizations have been pursuing CSIR and NBRI for the transfer of *Bt*-cotton developed at the institute. However, a lot remains to be done to ensure that the indigenously developed *Bt*-cotton reaches the field. Genes against multiple pests of cotton need to be brought together in Indian cultivars. Immunological and genomic methods need to be developed to facilitate rapid selection of the desired segregants. Thus accelerated development of Indian *Bt*-cotton that would succeed in long run, requires further partnerships among Indian research groups and more efficient coordination with the industry.

Slow pace of commercialization

There is a need to examine what can accelerate and ensure the progress of such laboratory-level achievements towards sustainable commercialization. Some of the technical reasons for the slow progress were briefly discussed earlier[13]. Transfer of the desired genes into crop species, with adequate expression levels in homozygous, true breeding lines is the first step towards the development of commercial 'product' (cultivar or hybrid). This requires selecting a large number of independent transformation events in a genotype suitable for regeneration, and identifying those with high and stable expression of the transgene. The next major stages are: integrating the desired transgenic trait with other acceptable agronomic and quality parameters through conventional approaches in plant breeding, food and bio-safety evaluation, multi-location agronomic performance trials and adequate seed production at all stages. Rapid progress through these stages requires the development of molecular approaches like immunological and marker-assisted selection methods for screening the segregating populations. Multiplication time can be saved using a combination of tissue culture and planting at multiple locations. Biosafety and performance evaluation requires close coordination among several institutes and organizations. Only after passing through these stages can the transgenic seeds be delivered to the farmers.

In moving forward at an accelerated pace, the following constraints are faced by researchers in public institutes, and seed companies:

- Lack of physical infrastructure in public-funded, non-agricultural research institutes and universities, where such transgenics have been developed.
- Different kind of competencies required for the development of marketable cultivars/hybrids. Most laboratories with capabilities in molecular genetics do not have prior experience in this kind of work.
- Original gene transfers are made as a part of multiple Ph D research programmes under a senior scientist. Their conversion to a marketable 'product' requires sustained efforts of the staff. Students and research scholars on fellowships do not find such work attractive.
- Traditionally, the administrators in public-sector research organizations and agricultural institutes have mindset limitations in the empowerment of scientists, moving ahead themselves with efficiency, making the required investments by developing expedient partnerships with industry.
- Small seed companies do not have the infrastructure to adopt physiological, molecular genetic and immunological tools required for efficient development, screening and selection of the desired transgenic lines. They can hire scientific personnel to carry out field experiments, but the manpower trained in the state-of-the-art molecular technologies is not easily available, and is much more expensive to employ. In general, they lack trained human resources, and facilities to carry out the molecular work needed to expedite the progress.
- GE technologies are intensively knowledge-driven. This makes it difficult for a majority of small seed companies to handle genes, transformations, analyse the associated IPR issues, and deal with regulatory depart-

ments. In spite of receiving a technically proven transgenic Coker line, even a large seed company like MAHYCO could manage these issues apparently due to its partnership with Monsanto, St. Louis.
- Food safety and bio-safety evaluation involves liaison with multiple institutes and high costs. Smaller seed companies and one-man-teams (with Ph D students and or project research fellows) of research scientists, as encountered commonly in India cannot handle these by themselves.

As a result of the above constraints, in spite of the national need and availability of technical capabilities, commercialization of the indigenously developed transgenics has not happened.

Cost of commercializing a new GE crop cultivar/hybrid

Development of a marketable GE cultivar/hybrid can be as expensive as developing a new drug, widely estimated at upward of US$ 800 million[14,15]. The overall cost for the development of a marketable 'product' is estimated to be at least 20-fold higher than the development of homozygous transgenic plants[16]. Some cost estimates for mandatory regulatory compliances are available[17]. The values range from US$ 700,000 for papaya to 2.25 million for rice and four million for herbicide-resistant soybean in Brazil. In terms of time, it took nearly 15 years for Monsanto to develop and get the first approval for commercial release of a *Bt* crop. The project concept existed in early 1980 and sufficient proof of concept had been published in the form of insect resistant transgenic *Bt*-tobacco[18,19] and tomato[20] by 1987. Yet, it was in 1995 that 'Bollgard' cotton and 'Maximizer' corn were released. The cost of developing the first transgenic R_o *Bt*-cotton line at NBRI under various components supported by the DBT, CSIR and NATP through the period 1995 to 2004 was about Rs 3 crores, inclusive of staff salaries. Given the advantage of the previously available published information, governmental infrastructure and some unaccounted overheads and concessions, this may be an underestimate. Nevertheless, industry may be able to achieve comparable goals in three- to five-fold higher cost in India. This is not a high cost compared to the estimates available from elsewhere. These estimates indicate the cost competitiveness of undertaking such projects in India. Hence, the opportunities are enormous and global, but can be realized only through strategically managed partnerships and efficient project execution. The *Bt*-cotton developed at NBRI requires at least another 5 years to introgress the gene into agronomically desirable backgrounds and obtain regulatory clearances before transgenic cultivars developed indigenously can be released for commercial cultivation. The partner industry immediately needs immunostrip-based kits against the novel protein designed at NBRI. They also need AFLP-based genomic screening to cut short the number of backcrosses.

Mission-mode approach

Synergizing partnerships and mission-mode approach are needed to expedite the development and commercialization of GE crops. A road map is needed for the exploitation of agronomically promising transgenic crop species already available (Table 1) from public-funded research in India. The following steps need to be taken:

(1) Compilation of agronomically useful genes and transgenics already available in the country and suitable for applications in different crops.
(2) Independent evaluation of GE stocks developed for the target trait, under containment conditions, if not already approved for growing in open field.
(3) Detailed examination of IPR issues.
(4) Examination from possible food and environmental safety viewpoint based on the literature.
(5) Wide publicity to the available stocks, along with the terms and conditions for transfer to private, and public institutions. Transformation of the genes and their pyramiding in priority crops.
(6) Compliance to the guidelines by RCGM and permission for growing transgenics in open field.
(7) Initiation of food and environment safety evaluation.
(8) Independent backcrossing programmes into agronomically acceptable genotypes by public ARIs, SAUs (public–public partnership) and private seed companies.
(9) Initiation of seed multiplication for bio-safety evaluation and field trials after 5–6 backcrosses to the recurrent parent.
(10) Initiation of bio-safety and agronomic evaluation of the selected gene–genotype combination.

The above aspects should be pursued in parallel, and by undertaking field work at normal and 'off season' locations. Taking *Bt*-cotton and male sterile *barnase–barstar* mustard, the first role models that would accelerate progress towards large-scale applications need to be developed and executed successfully.

A different kind of management and organizational structure is required to bring together the knowledge centres, plant-breeding laboratories, and small-scale seed industries. The ARIs and SAUs need to leverage the talent and materials available in non-agricultural institutions. Inflexibility of the systems often does not permit this even when there is a strong desire. Statutory rules are such that a plant molecular biologist cannot be recruited on faculty positions in most SAUs unless he/she holds a B Sc (Agriculture) degree. In the earlier days of the green revolution, National and State Seeds Corporations played a significant role in making available the seeds of new cultivars to the farmers.

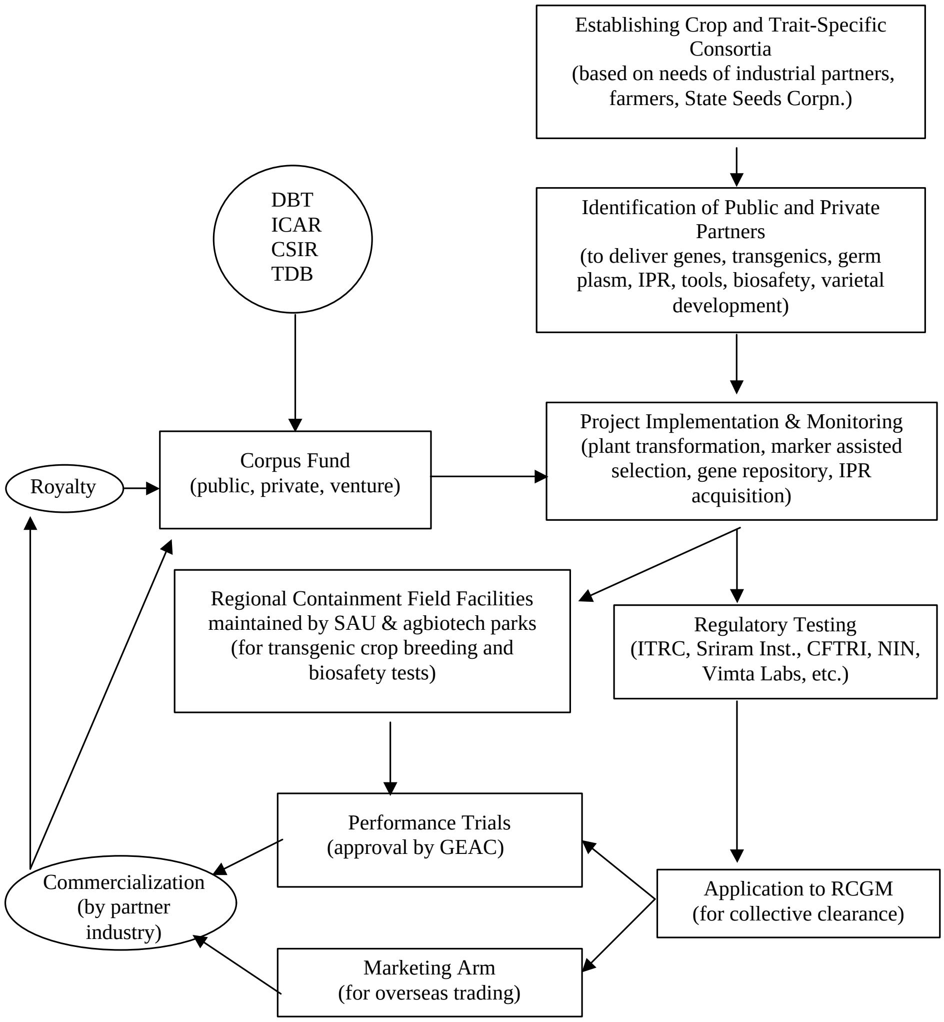

Figure 1. Networking plan for accelerating development and commercialization of indigenously developed transgenic crops.

However, most of the State Seed Corporations are currently operating with huge accumulated losses. Normally, one would expect some State Seed Corporations to venture into production and marketing of GE seeds. However, current experience shows that even the most enlightened ones have chosen to keep away for various reasons, including the uncertainties related to biosafety and regulatory issues, and the non-availability of indigenous transgenics. Establishment of an autonomous National Biotechnology Regulatory Authority, recently recommended by the Task Force may change this trend, provided an efficient single-window Government approval system is established.

Some examples of successful commercialization of complex technologies standardized through public-funded research into marketable products with back-up R&D support from leading research centres in the country are: Electronics Corporation of India, Nuclear Power Corporation Ltd, Haffkine Bio-Pharmaceutical Corporation Ltd, etc. These can serve as useful models for GE crops. Researchers in public institutions, private seed companies/agri-entrepreneurs need to join hands to form consortia aimed at crop-specific, goal-oriented commercialization projects. A governmental body is needed to provide a platform to bring them together. This may be done through a project execution structure of the kind developed by the Council of Scientific and Industrial Research under the NMITLI (New Millennium Indian Technology Leadership Initiative) programme for networking with industry. A representative functional plan for developing such consortia is given in Figure 1. All stake holders – Department of Biotechnology, Indian Council of Agricultural Research and Council of Scientific and Industrial Research – should initially support such joint endeavours with pooled financial resources, supplemented by the Technology Development Board. The Department of Science and Technology, New Delhi has established a few incubators in the country, a couple of them specifically for agri-biotechnology, such as the one at ICRISAT, Hyderabad. The facilities developed at these incubators can be used by the consortium on project-linked payment basis. The Task Force has also recommended Rs 12000 million additional fund during the remaining three years of the Tenth Plan. Support for mission-mode approach in such projects needs to be ensured till the stage of GEAC approval. Following the approval, successful initiatives would attract venture funds and larger investments for expanding seed production. The suggested approach would facilitate and expedite conversion of the laboratory accomplishments into crop cultivars/hybrids for the Indian farmers in short term, and perhaps open new overseas markets for the seed industry in future. A cess on seed sales can make such programmes financially sustainable in future, without Government support, to continually evolve globally competitive genes, transgenics, and technologies in response to the needs of the farmers.

After the acceptance of this article on 25 November 2004 we noticed a publication by Joel Cohen released on the net on 6 January 2005. The paper entitled ‘Poorer nations turn to publicly developed GM crops’, to be published in *Nature Biotechnology*, vol. 23, January 2005 considers on global basis, the issues that have been raised by us in this article in the Indian context. The readers would notice several commonalities in the issues raised and the approaches suggested.

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