Sustaining agbiotechnology through lean times

David McElroy

Most life science investors have historically shied away from supporting agbiotechnology, but changing consumer acceptance and refinements in infrastructure, intellectual property management and regulations may make the sector more attractive in the coming years.

US venture capital (VC) investment in biotechnology increased from less than 4% (of total VC funding) in 2000 (ref. 1) to 9% in 2002 (http://www.ventureeconomics.com). However, of those venture capitalists who claim a significant interest in the life sciences, only a handful have invested in agricultural or other industrial biotechnologies. Why has this situation arisen, what are the potential consequences for research, competition and economic growth in agriculture, and what can be done to rectify this state of affairs so that an innovative and robust industry can evolve to realize the full potential of agricultural biotechnology?

Opportunities abound

There is a broad spectrum of innovative product opportunities currently being addressed in agbiotechnology (see **Table 1**). These opportunities can be classified as meeting needs in crop productivity (input traits), food and bioprocessing (output traits) or nutraceuticals and pharmaceuticals (health or medicinal traits). There are also a number of genomics and enabling technologies that have applications in agbiotechnology.

Thus far, the majority of approved crops under cultivation are transgenic for input traits. Such traits (see **Table 1**) include genes for yield enhancement and pest control (e.g., Monsanto's (St. Louis, MO, USA) RoundupReady corn for tolerance to glyphosate-containing herbicides, and Monsanto's Bollgard *Bacillus thuringiensis* (Bt) cotton for lepidopteran insect control). These transgenic plant products generate economic benefit for farmers and retail consumers by lowering the financial and environmental costs of crop production. Input traits currently on the market represent alternatives to the products of the agricultural chemicals industry, such as sprays for insect control. The cost savings to farmers

David McElroy is at Verdia, Inc., 200 Penobscot Drive, Redwood City, California 94063, USA. e-mail: david.mcelroy@verdiainc.com
The views expressed here are those of the author and not the author's current employer.

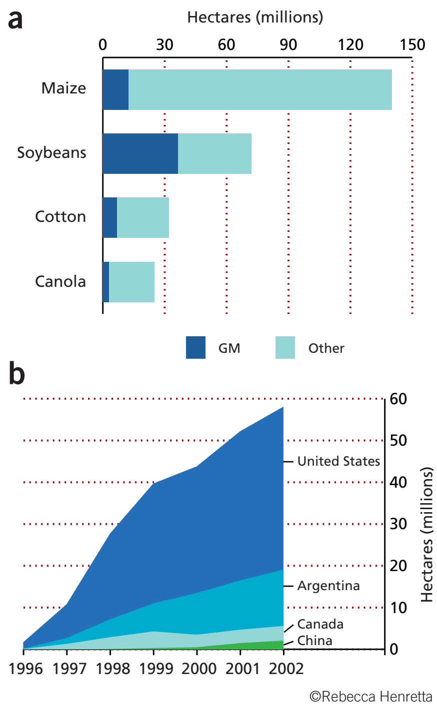

Figure 1 Worldwide area cultivated with transgenic crops. (**a**) Acreage in 2002. (**b**) Growth in acreage in the United States, Argentina, Canada and China, 1996–2002. Source: Clive James, ISAAA

associated with the use of agbiotechnology products can be readily calculated and consequently the pricing of these products at the producer level is relatively straightforward. Finally, a value sharing mechanism, involving a distribution (between seed companies and technology providers) of the technology access fees or seed premiums collected from the farmer-producers is already well established for this first generation of agbiotechnology products.

In the seven years since their first commercial introduction, transgenic crops containing input traits have been rapidly adopted in a number of important agricultural markets, and to date have been cumulatively grown on over 700 million acres (283.5 million hectares). In 2002 alone, 145 million acres (58.7 million hectares) of transgenic crops were grown globally, with an estimated market value of $4.25 billion (see **Fig. 1**).

Output traits include those for improving food and feed quality as well as those involved in food processing and bioprocessing (see **Table 1**). They target opportunities for differentiating commodity crop products, such as generating soybean plants yielding oil low in polyunsaturated fats. Output trait products (see **Table 2**) include the following: plants transformed with genes for commercially valuable oils (including lubricants), proteins and starches; plants transformed to alter fatty acid composition; plants transformed to modify seed storage proteins and amino acid profiles; and plants transformed to alter carbon-partitioning for novel starch production[2]. A first generation of output traits was commercialized in the 1990s, including products such as Calgene's (Davis, CA, USA; now part of Monsanto) FlavrSavr tomato with delayed fruit softening for longer 'on-the-vine' maturation and improved flavor (**Table 2**). However, this first generation of consumer-oriented products have all been withdrawn from the market because, for different reasons, they failed to capture enough value to warrant their continued production.

Even so, ongoing efforts to minimize financial risk within traditional agriculture continue to stimulate vertical integration within many agribusiness value chains, encourage contract growing with farmers to meet predefined product-quality specifications and promote an end-product orientation among producers with an associated focus on the measurement and categorization of crop-quality characteristics. The development of the next generation of transgenic output-trait products will aim to take advantage of these ongoing agribusiness developments, generating additional value by improving the specific measurable properties of commodity products to meet the cost, quality and health demands of increasingly sophisticated consumers. This new generation of output traits will have to do all of this in a manner that creates enough profit throughout each step of the product value chain to support their ongoing commercialization. For example, in the case of

Table 1 Product opportunities in agricultural biotechnology

Input traits	
Plant engineering/breeding	Crop transformation
	Trait expression/protection technologies
	Selective breeding technologies, e.g., genomic mapping/tracking
	Fertility control and apomixis
Pest control	Disease resistance
	Insect resistance
	Nematode resistance
	Herbicide tolerance
Yield enhancement	Plant biomass
	Crop and produce yield/quantity, *e.g.*, grain, fruit, fiber
	Abiotic stress tolerance
	Plant nutrition and water use
Output traits	
Food, feed and nutrition	Micronutrients, *e.g.*, iron, vitamins
	Protein composition and quality, *e.g.*, amino acids yield/profiles
	Vegetable oils/waxes, *e.g.*, quality, stability
	Carbohydrates, *e.g.*, starch/gums yield and quality
	Phytochemicals, *e.g.*, isoflavones, antioxidants
	Food quality, improved shelf life, reduced allergenicity/mycotoxins.
Food processing	Plants as expression/delivery systems for food enzymes,*e.g.*, lactase, lipase
	Enzymes for improved food processing and consistency, with reduced waste, *e.g.*, phytase, cellulase
Industrial processing	Bio-energy, *e.g.*, bio-ethanol
	Bio-catalysis
	Bio-fibers and bio-polymers
	Bio-sensors and bio-remediation
Medicinal traits	
Nutraceuticals and pharmaceuticals	Natural products, nutraceuticals, medicinal phytochemicals
	Therapeutically bioactive molecules modified *in planta*, *e.g.*, exploiting novelphytochemistry and/or processing
	Plants as expression/delivery systems for therapeutics, *e.g.*, edible vaccines, plantibodies

processed food products containing a transgenic output trait (e.g., a high solids tomatoes), benefit would have to be created and shared throughout a value chain that includes growers, processors, shippers, wholesalers, retailers and consumers.

Medicinal trait products include those containing genes that alter the yield/efficacy of nutraceuticals or pharmaceuticals derived from natural plant products, therapeutic molecules modified in planta or therapeutic proteins manufactured using plant production systems (**Table 1**). The 'plants-as-factories' opportunity purports to offer a flexibility of manufacturing scale at a lower capital requirement than competing production systems. As such, plants represent alternative manufacturing systems for a next generation of biopharmaceutical products that are reported to be facing a potential near-term crisis in manufacturing capacity[3].

In addition to these transgene-based trait opportunities there are a number of enabling and genomics technologies that are being used, among other things, for the discovery and development of products that are not genetically modified (GM) by plant transformation as well as the molecular marker–assisted breeding of both transgenic and nontransgenic crops. Advances in genomics technologies have led to an improved ability to identify targets for new agricultural chemical products, such as the discovery of new herbicide and insecticide targets. Others groups are using new enabling technologies to develop screening methods to better interrogate genomic diversity, including mutation-induced genomic variation, with a view towards developing novel non-GM products.

Why funding agbiotechnology goes against the grain

Given this broad range of consumer-oriented product opportunities, why have investors shied away from funding agbiotechnology? The fact that life sciences investors don't support agricultural opportunities cannot simply be due to a lack of familiarity with the research and development process in agbiotechnology. The activities and timelines for the agbiotechnology product development process[4] are similar to those for biopharmaceutical products[5] (**Fig. 2**). Furthermore, the cost of product development in agbiotechnology is significantly lower than that for biopharmaceutical products[6]. Investors might argue that, although the technologies and product development processes are similar (if not faster and cheaper) in agbiotechnology, the overall risk/reward profile for opportunities in medical/pharmaceutical biotechnology are always going to be more attractive than any opportunities in agbiotechnology. In contrast to healthcare and medicine, agriculture is perceived as a low tech, low margin, low cachet business.

Public perception and consumer benefits. As indicated above, there is a positive attitude towards transgenic crop products on the part of a farming industry that is constantly looking for ways to improve productivity and cut costs. However, resistance at the retail consumer level toward the first generation of input trait products, especially in Europe[7], has generated uncertainty concerning the wide-scale adoption and market acceptance of agbiotechnology products. Consumer acceptance may be less of an issue in the biopharmaceutical industry where the public appetite for new life-saving medicines remains undiminished, regardless of whether recombinant technology is used. The first generation of input-trait products in agbiotechnology has been widely criticized for conferring little or no retail consumer benefit. This is despite the fact that numerous studies have detailed the societal benefits of input-trait agbiotechnology products at both the environmental level (e.g., through improved soil and water conservation mediated by no-till agriculture associated with herbicide tolerant crops) and at the economic level (through improved farm productivity)[8–11]. It will be interesting to see how history reflects on why this consumer benefit story has not been more widely disseminated by an agrochemical industry purportedly seeking to peddle the first generation of agbiotechnology products.

Regulatory challenges. The evolving regulatory process for agbiotechnology products is disproportionately hampering the start-up end of the sector. The lack of a practical European framework to enable the commercialization of products derived from trans-

Table 2 Examples of output traits in transgenic crops

Crop	Phenotype	Benefits	Status	Company
Apple and melon	Altered fruit ripening	Delayed fruit spoilage	Approved for commercialization	Exelixis (S. San Francisco, CA, USA)
Soybeans	High oleic-acid oil	Reduced polyunsaturated fat content Reduce processing costs High oxidative stability Long shelf/frying life	Commercialized in 1997[a]	DuPont
Soybeans	Improved animal nutrition	Increased levels of amino acids (methionine and lysine) in meal	In development	Monsanto Pioneer Hi-Bred (DuPont)
Soybean	Altered stanol content	Cholesterol management	In development	Monsanto
Canola	High lauric oil	Replacement for coconut/palm oil	Commercialized in 1995[a] (Laurical)	Calgene (now Monsanto)
Canola	High stearate oil	Solid oil at room temperature Baking, margarine, confectionery foods	In development	Monsanto
Corn	Low phytate	Improved phosphorus availability Improved feed digestibility	In development	Monsanto Dow AgroSciences
Corn	Improved amino acid profiles	Increased levels of amino acids (tryptophan, lysine) in feed	In development	Monsanto
Corn	Altered oil profile and/or quality	Improved feed quality	In development	Monsanto
Corn	Increased starch level	Higher corn starch yield	In development	BASF
Cotton	Fiber pigmented	Reduce need for chemical dyes	In research	Monsanto
Cotton	Improved fiber quality	Improved fiber quality, *e.g.*, polyester	In research	Monsanto
Cotton	Improved seed oil	Improved feed quality	In research	CSIRO (Sydney, Australia)
Tomato	Delayed fruit ripening	Improved fruit maturation	Commercialized in 1994[a] (FlavrSavr)	Calgene (Monsanto)
Tomato	Delayed fruit ripening	Improved fruit maturation	Commercialized in 1995 (Endless Summer)	DNAP (Oakland, CA, USA; now BioNova)

[a]Subsequently withdrawn from market.

genic crops has restricted development to the adoption of new traits in US dominant row crops, such as corn, for which EU approval is unimportant for US exporters. Retail consumer demands for ever-increasing regulatory oversight of agbiotechnology products, although intended to allay concerns about the environmental safety of transgenic products, have created a significant financial barrier to entry for agbiotechnology startups, as well as for academic and government groups seeking to advance transgenic crop traits. The regulatory approval costs for agbiotechnology products are estimated to have increased from $5–10 million per transgenic crop product during the nineties to closer to $20–30 million today, as the extent of regulatory studies was expanded and codified, especially for obtaining international approvals for transgenic traits (my estimates, for major markets).

Increasing regulatory costs are contributing to a concentration of commercial agbiotechnology products in the hands of a small number of large agribusiness players. Ironically, this consumer advocate–driven regulatory barrier is further encouraging the development of the kinds of large corporate agribusiness that the very same groups complain about. Given the escalating costs of regulatory approvals, only products addressing opportunities in the large acreage crops (*e.g.*, corn, soybean, cotton and canola) can justify the required investment in gaining regulatory approval for transgenic traits. This hinders the exploitation of agricultural biotechnologies in the minor crops and restricts licensing opportunities for both private and public sector technology providers in these crops. This regulatory situation also excludes the public sector from independently participating in agbiotechnology product development, especially for those opportunities that are important to developing nations, many of which could well benefit from these new agricultural technologies. Escalation in regulatory costs will lead to the creation of two classes of crops: first, those large acreage crops able to financially justify the application of agbiotechnology and second, all other crops that cannot afford these costs.

Industry consolidation issues. Declining revenues in the agrochemical industry, in part brought on by the success of agbiotechnology products, has led to consolidation as agrochemical companies seek to maintain incomes by cutting costs, including rationalizing their merged R&D activities. In 1995, there were eleven large agrochemical companies with interests in agbiotechnology. Today, as a result of mergers, there are only six, and by 2004–2005 there may only be four large agrochemical companies left as Monsanto, DuPont (Wilmington, DE, USA), Dow (Indianapolis, IN, USA) and BASF (Ludwigshafen, Germany), each with net sales in 2002 of less than $3 billion, seek to exploit the economies of scale and scope currently afforded to Bayer (Leverkusen, Germany) and Syngenta (Basel,

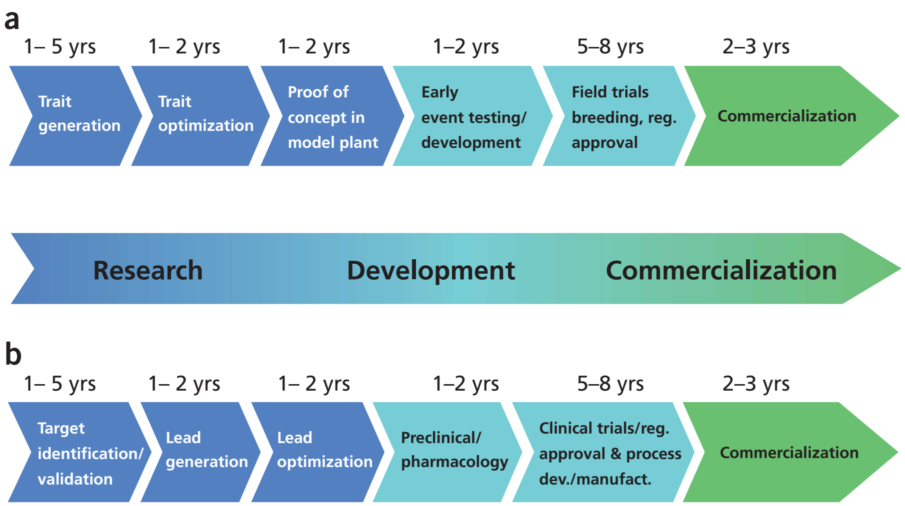

Figure 2 A comparison of the main activities and the timelines associated with the research, development and commercialization steps for product development in biotechnology. (**a**) Agricultural biotechnology. (**b**) Biopharmaceuticals.

Switzerland), each with net sales in 2002 of around $5 billion[12]. Consolidation means fewer potential agrochemical customers for both in-licensing new agricultural biotechnologies and acquiring the VC-funded startups that developed them. Consolidation has also made it harder for startups to do research deals with the major agrochemical companies as they work through their post-merger organizational issues.

The exit strategies for agbiotechnology startups had, in recent years, been almost exclusively confined to acquisition as the large agrochemical companies sought to obtain key enabling technologies and transgenic traits to combine with their newly acquired crop germplasm resources[13]. Examples include the acquisition of Calgene by Monsanto in 1996 and the acquisition of Plant Genetic Systems (Ghent, Belgium) by AgrEvo (now part of Bayer Crop Science) in 1997 (**Table 3**). However, with the current consolidation situation, and the agrochemical industry still looking to commercially exploit its first round of expensive agbiotechnology assets, the near-term exit strategies for new startups is becoming increasingly restricted. Coincidently, as a result of the recent history of agbiotechnology startup acquisitions, effectively no mid-level public companies currently exist in agbiotechnology. Consequently, there is very little analyst coverage of this space.

As a result of the public sector's historical propensity for providing the private sector with exclusive licenses to key agricultural biotechnologies (see p. 989), combined with the wave of agbiotechnology startup acquisitions in the nineties, a small set of large agrochemical players now controls much of the intellectual property (IP) covering those key enabling technologies necessary for the commercialization of agbiotechnology products[13]. Furthermore, much of the early IP protection afforded by the US Patent and Trademark Office (Washington, DC, USA) around agbiotechnology inventions involved broad claims. This challenging IP environment has been further aggravated by a recent history of IP exchanges to settle lawsuits between the large corporate agbiotechnology players. These developments have created a virtual cartel situation with respect to key IP in agbiotechnology. This situation significantly constrains the aspirations of VC-funded agbiotechnology startups, and public sector groups, that might be looking to 'go it alone' in advancing their own products.

Numerous studies have outlined the potential negative consequence for innovation and competition in the agriculture sector associated with ongoing consolidation in the industry[14,15]. A lack of VC investment will further aggravate this situation, as small innovative enterprises find themselves unable to fund the advancement of their own independent products. With the routes to funding agbiotechnology startups perceived as being especially challenging, entrepreneurs seeking a return on their 'sweat equity' may shy away from helping to build the kinds of opportunities that would make agbiotechnology a more attractive investment 'space.'

Infrastructure problems. Some analysts view output traits as a potential stimulant to both consumer acceptance and investor interest in agbiotechnology. Even so, several technical, infrastructure and commercial issues must be addressed to enable output traits to become commercially viable (see **Box 1**). Some of the issues associated with commodity output-trait products will also affect the commercial potential of nutraceutical and pharmaceutical products derived from the modification of natural plant pathways in transgenic crops. Finally, the realization of the 'plants-as-factories' business models for therapeutic protein production *in planta* is predicated on an expected near-term (2005–2010) capacity crunch in the pharmaceutical biotechmanufacturing industry[3]. Even if this biopharmaceutical capacity crunch turns out to be real, technical issues, regulatory concerns about the equivalence of plant-produced therapeutics, unknown timelines and development costs, an uncertain IP landscape and public perception concerns (*e.g.*, those exacerbated by the recent Prodigene incident involving the contamination of a soybean crop with potentially transgenic corn material producing a pharmaceutical protein, http://www.usda.gov/news/releases/2002/12/0498.htm) may still compromise the full realization of the 'plants-as-factories' opportunity. However, just one good success story in this area might lead to a flurry of investment activities (and startup exit options) as biopharmaceutical companies step in to embrace this opportunity.

The current state of affairs in startup agbiotechnology has led to the development of a virtual oligopoly situation with a small number of life science venture capitalists who, for various strategic reasons, still actively invest in the earliest stages of agbiotechnology. This is a disconcerting situation for both sides of the financing equation (investors and entrepreneurs) as any associated inhibition in agbiotechnology startup activity will result in a failure to generate the kinds of attractive investment leads that would justify more life science venture capitalists engaging in this space.

The agbiotechnology startup sector desperately needs investors who are not only willing to support initial rounds of financing, where companies might be looking for pre-money valuations of up to $25 million, but who will step up to invest in more mature agbiotechnology firms with valuations of $50–200 million. For such cases, investors would be looking to see these companies garner at least a $400 million market capitalization in a 7–10 year period. Investors do not appear to be convinced

Box 1 Valuing market opportunity for first-generation output traits in agbiotechnology

A number of issues currently compromise the potential value of any first generation of differentiated commodity output traits:

- Some nontransgenic specialty trait crops have been historically associated with reduced yield and unrealized profitability.
- The near-term technical inability of biotechnology/genomics to generate vastly differentiated quality traits in transgenic crops.
- The uncertain regulatory environment associated with agbiotechnology traits.
- The need for a business model, infrastructure and value-capture system that would facilitate the degree of cooperation between technology providers, growers and end users that would be necessary to successfully commercialize an output-trait product.
- The increased costs associated with any specialty handling/identity preservation systems that may have to be implemented throughout the production, processing and distribution chain for output traits. Such costs will be a function of specific product volumes and the degree of control required by the trait (that is, relatively low segregation costs for high-volume, low-value products, such as crops with improved amino acid profiles, versus potentially high identity preservation costs for low-volume, high-value products, such as plant-made pharmaceuticals).
- The current lack of validated production control systems for contract-grown, high-value, low-volume crops (*e.g.,* nutraceuticals and plant-made pharmaceuticals).
- The unavailability of suitable commodity testing and measuring systems at the rigid specifications needed to verify the desired quality characteristics of such output-trait products.
- The uncertainty associated with the availability of price discovery mechanisms for 'me-too' commodity output-trait crops. Currently, no industry-wide contract specification system exists for quality-trait crops in existing futures markets.
- The need for wide-scale implementation of contract-growing arrangements to mitigate producer's risk and to provide an incentive to grow new quality-trait crop products.
- Farmer apprehension about the effect on their independence of the tightly controled production and marketing channels that will need to be established to commercialize these differentiated commodity products.
- Future competition for crop output-trait products from synthetic alternatives, including those generated by alternative industrial biotechnology systems, such as recycled waste products via fermentation.

that agbiotechnology startups with this growth potential are out there today.

Encouraging investment in agbiotechnology

As most life science venture capitalists have historically not deemed it worthwhile to invest in building agbiotechnology practices, they consequently remain unfamiliar with the evolving risk/reward profile afforded by new opportunities in agriculture. Thus, given that investors (and analysts) are probably not tracking ongoing developments in this sector, they are not in any position to appropriately value emerging agbiotechnology companies or their products. What might happen to change the preconceptions such life science investors have about agbiotechnology?

Consumer-assessment of agbiotechnology benefits. Within the next 10 years, largely as a result of corporate and government investments today in genomics, we will have a greater understanding of natural product biochemistry in plants and we will be in a better position to manipulate plants to exploit such pathways for the production of improved nutraceutical and pharmaceutical products. However, marketing theory would suggest that the acceptance of such innovative technologies will require hands-on evaluation on the part of consumers who are fully aware of the transgenic nature of the products[16]. The agbiotechnology industry has been very successful in marketing its input-trait technologies to farmer-customers, including the provision of incentives to encourage the early utilization of these products upon their initial commercialization. Such proactive marketing is now required for the next generation of retail consumer-oriented agbiotechnology traits. Realization of the first examples of any next generation of consumer-oriented products might well benefit from the kind of private-public sector collaboration that we are seeing today in the development of 'golden rice' (a rice genetically engineered to produce elevated levels of β-carotene which, when converted in the human body, combats vitamin A deficiency). Alternatively, the next generation of output traits might stem from the application of nontransgenic gene knockout technologies to generate products such as allergen-free peanuts or decaffeinated coffee beans devoid of the genes for caffeine biosynthesis. The freedom of individual consumers to transparently assess the benefits of more affordable and/or improved quality products should act to develop a sustainable level of consumer-driven market demand for a next generation of products developed using agricultural biotechnologies.

Infrastructure developments. Improving consumer acceptance of agbiotechnology traits will draw an increasing number of commodity food company players toward the world of transgenic agriculture. Ongoing developments in agriculture with nontransgenic crops have already encouraged companies to develop the vertical integration, contract growing and end-product orientation necessary to take advantage of the next generation of transgenic crop products. Associated industry developments include the formation of Renessen (Chicago, IL, USA), a joint venture between Monsanto and Cargill (Minnetonka, MN, USA), aimed at better leveraging each party's capabilities to address opportunities in transgenic output traits across the agriculture value chain. In the same vein, DuPont and Bunge (White Plains, NY, USA) recently formed a joint venture, Solae (Fort Wayne, IN, USA), in part to develop transgenic output traits for soybeans. By vertically integrating under one corporate roof all of transgenic production, sourcing, marketing and distribution, new ventures such as Renessen and Solae seek to address many of the infrastructure issues currently compromising the widespread commercialization of transgenic output traits.

With the realization of these aforementioned developments an ever-increasing number of food companies may seek to obtain the new generation of consumer-oriented products emanating from agbiotechnology. Given that many of the established players in the food industry have been hesitant to date to embrace agricultural biotechnology, an opportunity exists for a new type of entrepreneurial food company to exploit the benefits conferred by improved output-trait products. Given the degree of regulatory scrutiny uniquely focused on transgenic crops, there is even an opportunity for this new generation of food companies to market the safety and quality aspects associated with any government 'approved' products derived from transgenic crops. New types of commercial partnerships between technology providers and food companies will both increase the deal flow and improve the exit options for entrepreneurial companies addressing new opportunities in agbiotechnology.

Private sector support. It is estimated that the agrochemical industry finances around 85% of the world's agbiotechnology R&D, currently running to around $900 million per year[17] . However, with the exception of Monsanto, the agrochemical industry has been relatively inefficient in discovering new agbiotechnology traits. An argument could be made that the big agrochemical businesses should scale back on their internal discovery and outsource this research to startup agbiotechnology companies, with the large agrochemical players focusing instead on product development, distribution and marketing. Of course this shift on the part of the agrochemical sector towards outsourcing research will work only if the investment community is willing to invest in supporting trait discovery and early-stage product development by startup agbiotechnology enterprises.

Government and public sector support. Given the current state of VC funding in agbiotechnology, local and federal government might, for strategic reasons, choose to kick-start the innovation process by altering tax structures to favor investment in innovation, developing infrastructure to support company incubation and directly investing (or coparticipating through strategic investment) in the development of entrepreneur-led agbiotechnology startups, investing especially in those startups focused on developing healthier, more nutritious foods. In the United States, state-led strategic investment in agriculture includes Iowa's $43 million TecTERRA Food Capital Fund, targeted at food processing and agricultural technology opportunities (http://www.cybus.com/), and the $503 million Grow Iowa Value Fund targeted at biotechnology, life sciences and value-added agricultural industries (http://www.ifbf.org/tif.asp). While still on the drawing board, other US states are beginning to channel revenue, such as

Table 3 Examples of agbiotechnology companies acquired by agricultural chemicals companies

Agchem acquirer	Agbiotech company	Date
Monsanto	Agracetus (Madison, WI, USA)	1995
	Calgene (Davis, CA, USA)	1996
Bayer (AgrEvo/Aventis)	Plant Genetic Systems (Ghent, Belguim)	1997
	PlantTec (Potsdam, Germany)	2000
Dow Agrosciences (Dow Elanco)	Mycogen (San Diego, CA, USA)	1996
Syngenta (Zeneca)	Mogen (Leiden, Netherlands)	1996
BASF	ExSeed Genetics (Owensboro, KY, USA)	2000

Tobacco Settlement Funds, toward supporting local agbiotechnology startups.

However, such startups will likely need several rounds of financing, not just seed funding, so governments will need to parse out their support and broadly encourage VC coinvestment to sustain successful startups through each stage of their development. There may even be a role for government (and other players in the public sector) in helping to mitigate some of the prohibitive costs currently associated with the regulatory approval of transgenic crop products, especially for startup products, for the exploitation of current agricultural biotechnologies in minor crops or for using these biotechnologies to address issues in crops of primary interest to developing nations. This can been seen in the establishment of the Agricultural Biotechnology Support Project by the United States Agency for International Development (Washington, DC, USA), which aims to support the development and commercialization of bioengineered crops as a complement to traditional and organic agricultural approaches in developing countries (http://www.absp2.cornell.edu).

Intellectual property issues. Government also has a role to play in controlling IP protection so as to fairly reward innovators for their investment while not overreaching to the extent that future innovation is inhibited. Recent developments in US patent law would support the notion that the US legal system is becoming less amenable to upholding broad patent claims[18]. Meanwhile, the public sector is beginning to realize[19] that if they are ever to exploit their own IP in the minor crops, including those that are important to developing nations, they will have to change the way they license their technologies to the private sector. A resulting increase in the granting of nonexclusive licenses by the public sector may make future IP more accessible to agbiotechnology startups. Furthermore, much of the fundamental IP in agbiotechnology was developed in the late eighties/early nineties and will soon be coming off patent.

Finally, those large agrochemical players that currently monopolize much of the IP in agbiotechnology may realize that if they are ever to see a next generation of innovative traits and technologies they will need to develop a more flexible licensing mechanism for allowing small startups access to their IP assets. Meanwhile, those few players that currently represent the agbiotechnology startup space need to realize that they can't wait for government or the agrochemical industry to get their act together and they must therefore do a better job of working together to advance their respective technology platforms and move their products toward the market.

Conclusions

Today, most venture investors, and even many industry participants, might be forgiven for being pessimistic about their ability to gain a competitive return in agbiotechnology. This is a result of a combination of factors, including the poor state of the agricultural economy, public acceptance issues associated with transgenic crops, a lack of a clear understanding of the future market potential for transgenic traits, and uncertainty over exit options for investments in agbiotechnology. This situation might well constrain near-term innovation and economic growth in the agbiotechnology sector. However, looking forward, several potentially beneficial trends are beginning to converge and the realization of these favorable developments may eventually help to improve the situation in agbiotechnology. The potential afforded by ongoing efforts in plant genomics will eventually deliver on the promise of generating both environmentally beneficial input traits and consumer-oriented output traits. Vertical integration in crop and food production chains will further enable the development of suitable value capture systems for output traits. Finally, the eventual establishment of a workable European Union regulatory process should provide an opportunity for the global commercialization of agbiotechnology traits across the significant remaining worldwide row crop acreage that is not currently planted with transgenic crops (**Fig. 1a**).

In the end, realizing a return on any investment is all about delivering a product that meets some unsatisfied customer need. No matter what consumers might say in market surveys about GM foods, for example, their actual behavior could be quite different if they were given the opportunity to try out products that satisfy their needs[16]. Ironically, many of the anti-GM consumer advocate groups that play lip service to the concept of 'consumer choice' have done everything they can to ensure that consumers are denied an opportunity to evaluate the benefits of genetically enhanced products. So someone is going to have to take the lead and proactively market GM food products to get them into the hands of retail consumers, despite the near-term conditions. If the established industry players are not up to the task then maybe insightful and pioneering investors should consider funding startups that have the fresh ideas and market maneuverability to take up the challenge.

ACKNOWLEDGMENTS
The author would like to thank John Bedbrook, Mike Lassner, Ken Moonie, Julie Geenty and Scott Thenell for their helpful comments and suggestions in reviewing drafts of this publication.

1. Gompers, P.A. & Lerner, J. *The Money of Invention* (Harvard Business School Press, Boston, MA, 2001).
2. Weck, E. The transgenic plant market: profits from new products and novel drugs (Drug & market development report no. 9070) (Westborough, MA, 2002).
3. Andersson, R. & Mynahan, R. The protein production challenge. *In Vivo: The Business and Medicine Report* **5**, 1–5 (2001).
4. McElroy, D. Moving agbiotech downstream. *Nat. Biotechnol.* **17**, 1071–1074 (1999).
5. Myers, S.C. & Howe, C.D. A life-cycle financial model of pharmaceutical R&D (MIT Program On the Pharmaceutical Industry working paper no. 41-97) (MIT Sloan School of Management, Cambridge, MA, 1997).
6. Demasi, J.A., Hansen, R.W. & Grabowski, H.G. The price of innovation: new estimates for drug development costs. *J. Health Economics* **22**, 151–185 (2003).
7. Fischhoff, B. & Fischhoff, I. Publics' opinions about biotechnologies. *AgBioForum* **4**, 155–162 (2001).
8. Gianessi, L.P., Silvers, C.S., Sanuka, S. & Carpenter, J.E. Plant biotechnology: current and potential impact for improving pest management in U.S. agriculture (National Center for Food & Agricultural Policy, Washington, DC, 2002).
9. Marra, M.C., Pardey, P.G. & Alston, J.M. The payoffs to transgenic field crops: an assessment of the evidence. *AgBioForum* **5**, 43–50 (2002).
10. Agricultural Biotechnology in Europe. Economic impact of crop biotechnology (Issue Paper 5) http://www.abeurope.info/images/files/abe_issues_paper_5.pdf (AgBiotech Europe, 2002).
11. Agricultural Biotechnology in Europe. The environmental impact of agricultural biotechnology (Issue Paper 3) (AgBiotech Europe, 2002).
12. Carson, D.D. Agricultural chemicals report (Merrill Lynch Research & Economics Group, New York, NY, 2002).
13. Graff, G.D., Rausser, G.C. & Small, A.A. Agricultural biotechnology's complementary intellectual assets. *Rev. Econ. Stats.* **85**, 349–363 (2003).
14. Brennan, M.F., Pray, C.E. & Courtmanche, A. in *Transitions in Agbiotech: Economics of Strategy and Policy*, Ch. 8 (ed. Lesser, W.H.) 153–174 (Food Marketing Policy Center, Storrs, CT, 2002).
15. Fulton, M. & Konstantinos, G. Agricultural biotechnology and industry structure. *AgBioForum* **4**, 137–151 (2001).
16. Phillips, P.W.B. & Corkindale, D. Marketing GM foods: the way forward. *AgBioForum* **5**, 113–121 (2003).
17. Graff, G.D. & Newcomb, J. Agricultural biotechnology at the crossroads. (Bio-Era report) http://www.bio-era.net/be_index.php (Bio Economic Research Associates, Cambridge, MA, 2003).
18. *Plant Genetic Systems v. Dekalb Genetics Corp.*, 2003 U.S. App. LEXIS 447 (Fed. Cir, Feb. 20, 2003).
19. Atkinson, R.C. *et al.* Public sector collaboration for agricultural IP management. *Science* **301**, 174–175 (2003).