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# Commercial plant breeding: What is in the biotech pipeline?

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#### Abstract

Of all of humankind's endeavours, agriculture has led to the most pressure on land, its resources and biodiversity. Over the past 50 years, the need to increase food production has resulted in the loss of one-fifth of the world's topsoil, one-fifth of its agricultural land and one-third of its forests. To slow down, and ideally reverse, this trend in the face of a predicted population increase of 50 per cent, a water shortage and climate change, new approaches will be needed. In this context, crop biotechnology and genomics have a major contributory role to play in the sustainable improvement of crop and livestock productivity, human and animal health and the development of renewable resources such as fibres, plastics, biofuels and plantmade pharmaceuticals. Manifestly, this will require both political will and international agreement.

'The further backward you look, the further forward you can see' Winston Churchill

#### INTRODUCTION

Despite wide-ranging controversies over many aspects of farming in both the developed and developing world, there is unanimous agreement that one of the main driving forces leading to pressure on land resources has been the need to increase food production.<sup>1</sup> The amount of land used by the first farmers 10,000 years ago was negligible. Today, with a population of approximately 6 billion, some 38 per cent of available land worldwide is used for cultivation or pasture.<sup>2</sup> Assuming no radical changes in human behaviour, the pressure on our environment will intensify with further population growth,<sup>3</sup> currently estimated to reach over 9 billion in the next 50 years. The problem continues to be most marked in regions of high biological diversity, where food security, health and poverty alleviation are already key priorities.1

Despite many valiant efforts, projections by the International Food

Policy Research Institute (IFPRI) suggest that under the most likely scenario, food insecurity and child malnutrition will remain widespread over the next 20 years.<sup>4,5</sup> Indeed, some 60 per cent of rural communities in the tropics and subtropics are affected by a persistent decline in household food production.<sup>6–8</sup> Technology, such as improved crop varieties and irrigation, has changed the situation for some people and, in consequence, demand for increasingly scarce water supplies is rising rapidly. However, since agriculture is in competition with industrial, household and environmental uses for this commodity, its availability for irrigation will be increasingly constrained. In fact, predictions indicate that while water extraction will increase by 50 per cent over the next 20 years, irrigation will increase by only 4 per cent, inevitably affecting food production.<sup>9</sup> At the same time the Earth is warming. Temperatures at the Earth's surface increased by an average of 0.6 °C over the 20th century. The 1990s were the hottest decade of the century; perhaps even of the millennium, and 1998, 2001 and 2002 were three of

The environment is under unprecedented pressure due to population increase

All farming practices impact the environment

More sustainable farming systems are needed

Crop biotechnology and genomics have a part to play in reducing agricultural intensification the hottest years ever recorded.<sup>10</sup> The growing scientific consensus is that this was largely the result of emissions of carbon dioxide and other greenhouse gases from human activities, including industrial processes, construction, fossil fuel combustion and land use such as deforestation. Projections of future warming suggest a global increase of 1.4–5.8 °C by 2100, with warming in the USA expected to be higher. This warming, along with the associated changes in precipitation and sea level rise, will have important consequences for the environment and economy.<sup>10</sup>

Clearly such trends are unsustainable and one major responsibility of the scientific community is to demonstrate the options that will be available for future policy makers. <sup>11</sup> If progress is to be made, as it was in the case of the Green Revolution, polarised views and extended debate over the use of less intensive alternatives such as the cultivation of GM crops will need to be set aside in favour of decision making and action. <sup>12</sup> This requires political will.

Fortunately, agriculture is no stranger to innovation. Since the beginning of time, people have sought to improve the yield, quality, variety and availability of food, non-food crops and livestock<sup>13</sup> (Table 1). While many new ideas have evolved from farmers' observations, or by landowners introducing new practices such as the use of turnips to over-winter cattle, others were introduced as adaptations of approaches used abroad,

**Table I:** A brief history of agriculture

4,000,000 BC	First hunter gatherers	
10,000 BC	Organised cultivation of crops	
7,000-5,000 BC	Domestication of plants (wheat/flax) and animals	
AD 1400	Winter food crops	
1694	Discovery of sexual reproduction in plants	
1866	Mendel – the basis for modern breeding	
1900	Hybrid maize (USA)	
1927	Mutation via X-rays (Golden Promise barley)	
1950s	1950s Green Revolution – high input and yield	
1990	First GM crops	
	·	

such as the Laloux strip system for pesticide spray application. Not all changes were universally welcomed, such as when tractors began to replace horses or when the steel plough – initially held to poison the ground – were first adopted. Things are little different today.

In consequence, global agriculture has become highly diverse, ranging from socalled 'conventional' high-productivity systems to low-input and organic farming systems, often co-existing to different degrees. Their evolution reflects economic, social and cultural developments that are inextricably intertwined. Regardless of the growing system employed land must be brought under the plough and with some 35-42 per cent of the world's food and fibre lost to pests<sup>5,14,15</sup> it is not possible to achieve reasonable agricultural productivity without significantly affecting the environment. Every choice involves different fundamental trade-offs between advantages and disadvantages (Table 2), though all with the same objective, that is to win food for people by beating the competition of weeds and pests and abiotic factors such as drought. As an old adage puts it,

One for the rook, one for the crow, One for to rot and one for to grow.

Looking forward, the major challenge to agriculture and the main driver for modern crop development are the need to balance (1) the provision of an adequate food supply in the face of a globally expanding population with (2) resultant environmental impact from urbanisation, habitat loss, the impact of introduced species, water shortage and climate change. To achieve this, existing practices must be adapted and new solutions developed that will allow the improvement of farm productivity and food quality with lower environmental impacts. This is where many believe that crop biotechnology and new genomic methods such as marker-assisted breeding can help to play a major role. When

Table 2: All farming systems involve trade-offs

Farming type	Positive	Negative
Conventional	High productivity	High input, pesticide, fertiliser, ploughing (energy), irrigation
Marginal (low input)	Low input	Uses a lot of land, often in high-biodiversity areas
Organic	No artificial fertiliser	High use of manure and old pesticides, eg copper

considering the potential of GM crops, two questions need to be asked:<sup>16</sup>

GM crops which require lower inputs, eg less spraying, are particularly suited to small-scale farmers

- Does the new GM crop replace an existing technology or practice that is more harmful to the environment or human health?
- Does the new GM crop address a problem that has not been solved by existing research?

It must also be recognised that there are both similar and differing needs between the developed and developing world. One of the attractions of first generation GM crops is their 'scale neutrality'. This means that because the seed already contains the gene(s) coding for a desirable agronomic trait, for example, pest resistance via Bt protein, it is as simple for the smallholder to use as for large-scale farmers. This is not true in the situation of conventional agriculture where significant investment in equipment and protective

Farmers and breeders have selected varieties with the best genetic traits since time began

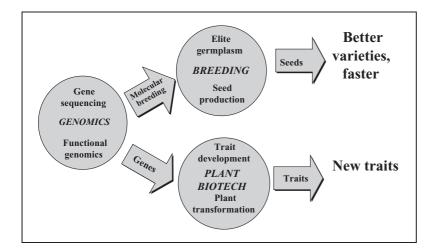


Figure 1: New tools for discovery: chemistry to biology

clothing are required for chemical spraying.

#### INNOVATION IN AGRICULTURE: THE CONTRIBUTION OF BIOTECHNOLOGY

Today, to develop better crop varieties, breeders and scientists have used an array of tools, ranging from artificial crossing (hybridisation) to mutagenesis, radiation breeding, embryo rescue and somaclonal variation, for example.<sup>17</sup> Research in the 1970s and 1980s led to the first transformed crops using modern biotechnology by the early 1990s.

Traditionally, biotechnology involves the use of biological organisms to provide food, clothes, medicines and other products;<sup>18</sup> good examples are the production of beer using yeast or antibiotics using fermentation techniques involving fungi or bacteria. Modern biotechnology, more commonly referred to as genetic modification (GM) or genetic engineering (GE), allows researchers to remove individual genes from one species and insert them into another without the need for sexual compatibility. When applied to agriculture, this technology enables step changes in the characteristics of given plants, conferring new traits such as pest/ disease/stress resistance, herbicide tolerance, improved nutritional qualities or the ability to produce biological materials in plants, for example (Figure 1). GM technology is also greatly aided by the science of genomics, the process of mapping, sequencing and analysis of DNA to characterise, determine function and understand how gene products interact (Figure 2).

Medern biotechnology and genomics are a natural development from the discovery of the structure of DNA in 1953

Genome Gene sequence Gene Plant traits Gene map expression Yield Drought G C G T G T Disease  $\triangle$   $\bigcirc$   $\triangle$   $\bigcirc$   $\bigcirc$   $\bigcirc$   $\bigcirc$ Stress (C) (T) (A) (G) (C) (C) (G) (A) (C) (T) (A) (G) TCGACG Oil quality (A) (T) (G) (C) (A) (A) A T G C TDisease Yield Maturity Yield **Bioinformatics** Genome Sequence **Function Product** 

Figure 2: The role of genomics in the discovery of new agricultural traits and products

Agricultural biotechnology has been very rapidly adopted by farmers in developing as well as developed countries

The agricultural biotechnology pipeline contains three generations of products

Agricultural biotechnology has been the single most rapidly adopted technology in the history of agriculture. Since their first commercialisation in 1996, GM crops increased from 1.7 to 67.7 million hectares worldwide by 2003 (Figure 3). Although heavily contested in certain parts of the world, agricultural biotechnology is proving to be an invaluable new tool in the development of crop varieties adapted to local needs, both in the developed and developing world, providing on a case-by-case basis benefits for farmers, consumers and the environment. <sup>13,19</sup> Examples of GM crops

with relevance to developing countries are discussed in detail by the Nuffield Council on Bioethics.<sup>20</sup>

When developing new varieties using the tools of modern biotechnology, researchers and seed breeders first seek to identify unmet needs that are difficult to resolve or cannot be addressed using conventional methods. After the necessary thorough evaluation of human and environmental safety by national and international authorities before regulatory approval can be given, the free market then decides whether the new products are of value or not.

## 52.6 58.7 27.8 27.8 29.9 2000 2001 2002 2003

**Figure 3:** Global plantings of GM crops (millions of hectares) Source: ISAAA, URL: http://www.isaaa.org

## THE AGRICULTURAL BIOTECHNOLOGY PIPELINE

Since crop biotechnology began, research has been conducted on a very wide variety of crops and traits. Three 'generations' of products can be distinguished: (1) a first generation carrying agronomic traits, designed to make crops easier or better adapted for farmers to grow, (2) a second generation carrying quality traits impacting on the nutritional value of food and feed and (3) a third generation using plants as production systems for pharmaceuticals and renewable industrial compounds

First generation products contain agronomic traits which make crops easier to grow for farmers (Figure 4). The different 'waves' of products are not strictly sequential in time; for example, stress resistance, which is well advanced though still in research, but constitutes a first generation product.<sup>21</sup>

The following sections will provide examples of agricultural biotechnology products in each of these categories (Figure 5).

### First generation products: current and future agronomic traits

Crops with protection against insect attack (corn, cotton and potato), tolerance

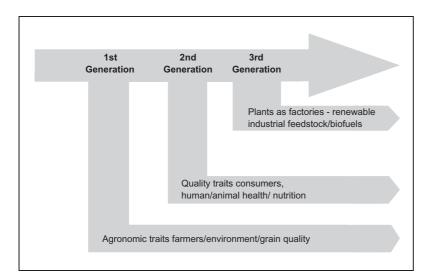
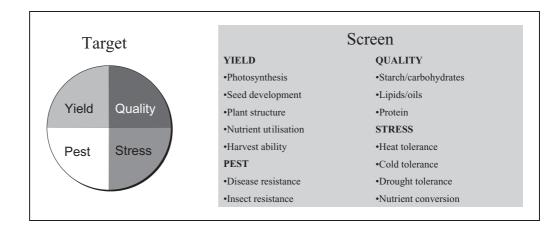


Figure 4: The agricultural biotechnology pipeline

to herbicides (corn, cotton, soybean, canola) or a combination of both are the major agronomic traits found in the marketplace today. <sup>19</sup> These crops have been rapidly adopted by farmers in the developing and developed world <sup>19</sup> and provide wide-ranging benefits by reducing pesticide use, increasing yields and having a significant economic impact on agriculture. <sup>22–26</sup>

Traditionally, tillage of soil has been used as the primary means to control weeds. However, this can also lead to soil degradation by causing erosion, reducing soil quality and harming soil organisms. Once effective herbicides were developed in the second half of the 20th century, farmers began to reduce their dependence on tillage. Tillage systems are classified according to how much crop residue is left on the soil surface. Conservation tillage is defined as 'any tillage and planting system that covers more than 30% of the soil surface with crop residue, after planting, to reduce soil erosion by water'. 27 The development of GM crops modified to be tolerant to herbicides has provided new tools and practices for controlling weeds and has accelerated the adoption of conservation tillage, low-till or no-till practices. In America, more than onethird of all soybeans are grown without ploughing mostly due to the introduction of Roundup Ready® varieties which are resistant to the broad spectrum herbicide,



**Figure 5:** First and second generation biotechnology traits

Agricultural biotechnology facilitates no-till systems which return humus to the soil and reduce the energy consumption (hence co<sub>2</sub> release) of ploughing

Insect resistance traits have led to a significant reduction in chemical pesticide use

Virus resistance traits have had important socio-economic benefits, especially in developing countries

Crops are being researched which will be heat, drought, saline and cold tolerant

glyphosate. No-till farming practices can also be applied to cotton, and, in the USA, 80 per cent of growers are making fewer tillage passes and 75 per cent are leaving more crop residue.<sup>28</sup> This is better for the soil and reduces energy usage.

Progress with agronomic traits is in constant evolution. As an illustration, several new crop varieties intended to combat agricultural pests were introduced in 2003. These include new maize varieties expressing a novel Bacillus thuringiensis insecticidal protein that controls the most damaging US corn pest<sup>29</sup> corn rootworm. This product is designed to deliver economic benefits to the grower while reducing the levels of insecticides traditionally used to drench the soil.<sup>30</sup> A new product with improved efficacy against a broader range of lepidopteran pests has been approved for use in US and Australian cotton production.<sup>31–34</sup> This product is significant in that it expresses two insecticidal proteins, thus improving efficacy and also aiding insect resistance management strategies in cotton. Turning to herbicide tolerance, a number of additional crops with tolerance to glufosinate,<sup>35</sup> bromoxinyl<sup>36</sup> or glyphosate<sup>37</sup> will be commercialised in the next five years.

A third type of agronomic trait currently available only through biotechnology is resistance to viruses, often introduced into crops such as papaya, cassava, squash and potato that are especially relevant for developing countries. To date, they are grown only on a relatively small number of hectares. 19 Sweet potato resistant to sweet potato feathery mottle virus is in development and has great potential to increase yields in Kenya. 38,39 Papaya resistant to the papaya ringspot virus (PRSV) was commercialised in Hawaii in 1997 and locally adapted varieties are being worked on for South-East Asia where resourcepoor farmers are heavily affected by PRSV.40

Yield is a critical factor in measuring

the success of most crops. Crop yields are depressed by such biotic stresses such as weeds, insects and pathogens. Current research efforts are focusing on such abiotic stresses and is proving very successful. Abiotic stress tolerances are of particular importance in the light of increasing water shortages and global climate changes. These traits are being actively pursued as a means of preserving yield under these diverse environmental conditions. 41,42 Among the targets being researched are tolerances to cold, 43,44 heat, 45 drought and salinity. 46-48 In the case of salinity resulting from the evaporation of irrigation water, about 10 million hectares of land are lost annually. 49 These products have potential to aid farmers in the well-developed agricultural economies as well as in the developing world.

Improvements in yield are also being pursued by changing the innate characteristics that may impact on the yield of a crop plant. Efforts are underway to influence fundamental physiological processes such as biomass accumulation, photosynthetic capabilities, nutrient absorption and utilisation. Genomics is a key enabler in pursuing these traits, which tend to be multigenic in nature.

Without yield improvements that may help to constrain the agricultural 'footprint', it is predicted that over the next 50 years, a third of all remaining natural tropical and temperate ecosystems could be lost to agriculture.<sup>50</sup> Historic precedent and present land availability indicate that almost all new conversion will be in South America and sub-Saharan Africa. More than half of the sustainable crop land is found in just seven countries - Angola, Argentina, Bolivia, Brazil, Columbia, Democratic Republic of Congo and Sudan<sup>51</sup> – five of which are among the most biodiverse in the world; the remaining two, Angola and Sudan, are both considered highly diverse. Much of the conversion will be of large blocks of forest affecting dependent species often with small ranges. Such forest loss and fragmentation will have a

Yield improvements and the ability to reuse marginal farmland are vital to constrain the agricultural footprint and preserve biodiversity

Delays in GM acceptance in Europe have led to the retention of high input and less environmentally friendly farming practices

Second generation nutritionally enhanced foods resulting from crop biotechnology will become a major weapon against preventable human disease

Foods will be modified to remove allergens and toxic substances

disproportionately high impact on global biodiversity.<sup>52,53</sup>

Using extinction as a tangible measure of biodiversity loss, and with a range of caveats, assessment of extinction risk in birds carried out by BirdLife International – using the World Conservation Union's Red List of Threatened Species – has concluded that perhaps 350 species (3.5 per cent of the world's birds) might disappear between now and 2050.<sup>54</sup>

In the next five years, most commercialised plant biotechnology products will continue to be input traits that protect the crop from damage and confer improved agronomic properties of benefit to the farmer such as higher yields, while at the same time benefiting the environment through lower chemical inputs, water and energy use. It is unfortunate that consumers do not obtain direct benefits from the first generation of GM crops as this has slowed acceptance in regions such as Europe, which indirectly results in the retention of less environmentally friendly higher-input farming practices among certain trading partners.

#### Second generation products: current and future improved food and feed quality traits

Although agronomic traits are dominant in agricultural biotechnology today, ironically the first trait to be commercialised was a quality trait. Antisense technologies were used to suppress early ripening, generating a tomato with delayed ripening and hence improved quality and flavour for the customer. The Flavr Savr® tomato was the first commercialised GM crop, introduced in 1994 in America by Calgene. In the UK, Zeneca developed a double concentrated paste from GM tomatoes which was marketed by the Sainsbury and Safeway stores in 1996. The product enjoyed some success but never established a cost-effective supply or viable market in the USA. While very successful in the UK, it was withdrawn

following intervention by the opponents of GM food.

Significant savings to health budgets could be achieved in the medium to long term with proper investment in diet and health. It is increasingly being realised that diet and nutrition should be a key component of any preventative health strategy to help counteract an escalating incidence of diseases such as type 2 diabetes, obesity, some cancers, cardiovascular and osteoporosis. In the UK, obesity has doubled in children in the past ten years. Increasing public awareness of the proven effects of nutrients on health promotion and disease prevention provides a rationale for introducing new approaches to chronic disease through modification of diet and lifestyle, although it is argued that this needs to be given more prominence by governments.<sup>55</sup> In parallel with this upsurge of interest is the importance of proper regulation, which is of equal importance to consumers and industry alike. Proposed regulations cover health claims, prevention claims, reduction of disease risk claims and nutrient claims, EU COM (2003) 424 final<sup>56</sup> and PASSCLAIM.<sup>57</sup> The FAO/WHO report on Diet, Nutrition and the Prevention of Chronic Diseases<sup>58</sup> highlights four prerequisites for effective strategies – leadership, effective communication functioning alliances and partnerships, and an enabling environment.

In recognition of the potential impact of diet and nutrition on health, a number of food and feed products with safer or enhanced quality or nutritional properties are in the pipeline. <sup>42,59,60</sup> They fall into four main categories.

#### Lower or removed antinutrients/allergens

Various targeted GM approaches involving antisense RNA and gene 'knock-out' techniques are being used to reduce or remove toxic components within food such as anti-nutritional factors or protein elements responsible for allergenic responses in foods such as peanuts, <sup>61</sup> soya, <sup>62</sup> rice <sup>63</sup> and wheat. <sup>64</sup>

These new products with improved quality or nutritional profiles will offer direct benefits to the consumer by providing safer and healthier food in the marketplace.

Enhancing health-promoting substances

It was Hippocrates (470–410 BC) who made the connection between food and health, stating: 'Let thy food be thy medicine and thy medicine be thy food'. Oils are an important dietary component but can also be linked with cardiovascular disease. Plant biotechnology has successfully altered fatty acid compositions of major oilseed crops to produce oils with improved processing characteristics or oils with enhanced nutritional characteristics. 34,65–67 For example, increasing the level of oleic oil (a monounsaturated fatty acid) in rapeseed oil and soyabeans reduces the level of trans and saturated fat intake with measurable cardiovascular benefit.<sup>68</sup> Omega 3 fatty acids have a potent cardio-protective effect but their main source has been from fish oil. With changes in the dietary habits, Omega 3 intake is sub-optimal in a number of population groups. Recent research had led to the expression of plant genes coding an Omega 3 fatty acid in seed oil crops with the expectation that vegetable oils will in future be able to provide a supplementary source of Omega 3 fatty acids in the diet.

Specific proteins, such as human lactoferrin and lysozyme, are being expressed in rice to produce infant formula more similar to human milk.<sup>69</sup>

#### Vitamins and micronutrients

Traits for animal feed include maize and soy with increased levels of essential amino acids or improved oil composition that can reduce the needs for dietary supplements. To,71 Lysine and methionine levels are two such essential amino acids whose levels have been increased using biotechnology. Nearly one-sixth of the global population of 6 billion people do not have adequate diets, and micronutrient (vitamin and mineral)

deficiencies are common. Solutions are often limited because of poor agricultural productivity and a shortage of income to buy foods. In consequence, vitamin and mineral enhancement are prime targets with particular importance to the developing world. Rice with increased levels of beta-carotene to address vitamin A deficiency has been generated and is currently in the advanced stages of testing.<sup>73,74</sup> Canola with increased levels of beta-carotene in its oil has also been produced,<sup>75</sup> and this technology is being transferred for use in mustard, another key staple in India where vitamin A deficiency is also prevalent.<sup>76</sup> Vitamin E content in plants has also been enriched<sup>77,78</sup> in rice. In addition other grains with enhanced levels of minerals are currently in development.79,80

Nutritionally enhanced crops for livestock production

The burgeoning population increase together with a trend to urbanisation in developing countries implies a doubling of animal protein production and a corresponding doubling of feed grains;81 for per capita meat consumption is highly correlated with national income. Moreover, since meat and bone meal (MBM) was banned in Europe as a nitrogen source, alternative crop-based (largely soya) proteins have become essential to fill the shortfall. Limitations to efficient livestock production are numerous (Figure 6), and besides low genetic potential of the stock include crop factors such as inadequate feed supply (often due to extremes of climate) and quality (due to the presence of antinutrients and mycotoxins) as well as deficiencies in specific nutrients (eg amino acids and minerals). 82,83 With an estimated demand for livestock products projected to increase by 3 per cent per year in developing countries, there needs to be a very significant increase in both yield and quality of feed resources including forages, cereal grains and oilseeds. A major challenge is to achieve this while attempting to decrease the

GM foods can provide essential vitamins and even vaccines to combat serious diseases in developing countries

Increased urbanisation in developing countries is linked to increased meat consumption which will double grain requirements over the next 20 years

GM is being used to increase the levels of essential amino acids for animal nutrition

#### **TRAIT**

- •Low phytate soy and maize
- •Low fibre feeds (monogastrics)
- •High oil maize
- •Higher essential amino acids
- •High oleic soy
- ·Low stachyose soybeans

#### **BENEFIT**

- ↑ Phosphate utilisation
- ↑ Digestibility ↓ manure/gas
- ↑ FCE ↑ lipid profile
- ↑ Feed value
- ↑ Saturated fat and trans fatty acid
- ↑ Sugar and energy







**Figure 6:** Livestock production opportunities via GM (FCE = food conversion efficiency)

combined environmental impact of crop and animal production. 84 Biotechnology may be the best available tool to make a significant impact in these areas. Maize grain is generally the preferred energy supplement for livestock production systems and soyabean is usually the preferred protein supplement. Cereals are often low in lysine and legumes in the sulphur-containing amino acids methionine and cysteine. Modern biotechnology is being used to modify such amino acid profiles with the aim to remove the need for dietary supplementation. 70

Efforts to improve the nutrient density of livestock diets by the use of non-structural, readily digestible starches and oils<sup>71</sup> provide an important route to improve food conversion efficiency while reducing the impact of excreta on the environment. For example, high oleic acid soyabeans can contain more than 80 per cent oleic acid in their oil compared with 24 per cent for traditional soyabean oil. Research has indicated that feeding high oleic full-fat soya to cows and chickens provides not only an efficient energy source but may result in a

lowering of saturated fat levels in milk and poultry meat. 68,85,86 Work is also in progress on crops that will have improved nitrogen digestibility or those with high phytase or low phytic acid content.87 Both developments will be a major factor in reducing nitrogen and phosphorus excretion and hence pollution of the soil and watercourses. With predicted threefold increases in parallel in the use of nitrogen and phosphate fertilisers to boost conventional food production, fresh water and marine ecosystems will be under major threat from eutrophication without the application of novel approaches.

## Third generation products: current and future crop production systems

Plant biotechnology can be used to create crop plants that serve as natural, renewable production systems. One potential market opportunity is the production of enzymes that are used in detergent formulations, industrial processes or in food manufacturing. Plant-based biopolymer production for degradable and recyclable packaging is

Transgenic feedstuffs are under development which will reduce nitrogen and phosphorous pollution of the soil and water courses by livestock Third generation biotechnology allows you to move from chemical plants to green plants for the production of renewable industrial feedstock and fuels

Transgenic plants can be used for bioremediation of soils

and water courses

Biotechnology is a new tool in the agricultural toolbox which is already delivering valued benefits to health, the environment, the economy and farmers another area being pursued in the laboratory. Also, significant progress has been made for the use of plants for pharmaceutical purposes: this is known as biopharming or molecular pharming. This work includes both the production of therapeutic proteins in crop plants<sup>88</sup> as well as the production of edible vaccines. <sup>89–93</sup>

#### Bioremediation

Heavy metal toxicity poses major environmental and health problems. Removal of heavy metals from contaminated soils and waters is costly and inefficient. Recent studies have suggested that metal uptake into plant roots can provide an effective approach for bioremediation of metal-contaminated waters and soils. Phytochelatins play major roles in metal detoxification in plants and fungi and have been proposed to be central to heavy metal accumulation. By screening for plant genes mediating metal tolerance, different laboratories have now independently identified a new gene family whose expression results in a dramatic increasing in cadmium tolerance. Detailed analyses have shown that these genes encode phytochelatin synthases (PCS). Disruption in a yeast PCS gene results in hypersensitivity to Cd<sup>2+</sup> and Cu<sup>2+</sup> and inability to synthesise phytochelatins upon Cd<sup>2+</sup> exposure. These data demonstrate that PCS genes mediate phytochelatin synthesis and metal detoxification in eukaryotes and suggest that PCS genes, expressed synergistically with other genes, could be useful for engineering plants for removal of heavy metals from contaminated soils and waters.94-97

While commercial introduction of these traits is several years away, the promising results already being seen in the laboratory are a real encouragement for the future applications of biotechnology in using plants as a modern, efficient way of molecular farming. Additional efforts are focused on using plants or plant-based products with enhanced levels of sugars as fermentation sources for efficient

production of ethanol and other replacements for petroleum-based products. Such applications would reduce dependence on non-renewable sources of energy and encourage more environmentally friendly 'CO<sub>2</sub> neutral' sources of fuel products which would go some way towards meeting European Union targets of 18 million tonnes of biofuel by 2010.<sup>98</sup>

#### IMPLICATIONS OF BIOTECHNOLOGY FOR THE FUTURE

Present agricultural practices are unsustainable and many are leading to environmental damage. Furthermore, in the light of an increasing global population, and urbanisation with its attendant impacts, environmental pressures are set to increase. Throughout history, technology has been integral to the advancement of the world, for example, fire, the wheel, electricity and the microchip. Today, biotechnology is a new frontier and the careful application of this technology in combination with both traditional and new developments of existing farming practices offers a means to slow down and possibly reverse the extent of current environmental damage.

As with any innovation, the costs of proceeding need to be weighed against the costs of the non-use of GM. Nothing has driven more species to extinction than the development of an agriculture to feed 6 billion people. To assert that today's GM crops per se are a threat to biodiversity is not correct. Indeed, the recently reported UK Farm Scale Evaluations (FSE)<sup>99</sup> recognised that it was the herbicide regimes employed rather than the crops themselves, whether GM or non-GM, that led to indirect effects on biodiversity. In essence, more weeds result in more wildlife. The use of GM crop-herbicide combinations give considerable flexibility to develop weed control strategies that favour wildlife compared with conventional herbicide sprayings. 100 For example, the use of GM insect-protected crops or those tolerant to

In many cases the GM crops enable less chemical use with more benign herbicides

More environmentally friendly methods of agricultural production, such as agricultural biotech, are essential to reduce environmental degradation

Full life cycle analysis shows a large number of savings for the environment if GM crops like sugarbeet were to be adopted

With agricultural biotech we now have the capability to meet the diverse needs of expanding populations with lower environmental impact less toxic herbicides provides the opportunity to significantly reduce both the number of different pesticides often applied in tank mixes, as well as the number of repeat sprayings traditionally required for pest and weed control. Looking in detail at the broader life cycle analysis (LCA) impacts of pesticide reduction in the case of GM sugarbeet, namely fewer chemical production plants, less raw material, energy and plastic packaging, less diesel fuel for distribution and spraying and less chemical into the biosphere already shows lower comparative environmental and human health impacts. The LCA modelling involves ISO 14040, which is a recognised international standard. 101

So in the face of an unprecedented increase in the pressure on delicate agroecological systems, genomics now gives us a choice. We can use the new tools it has provided to help offset agricultural intensification and reduce environmental degradation or we can bury our heads in the sand and trust that the problem will go away. As with any new technology it is necessary to proceed prudently and cautiously. Nevertheless with major and potential far-reaching demographic changes upon us it would be perverse to ignore more environmentally friendly methods, including biotechnology, which help to build sustainable and productive lowagricultural input systems in appropriate situations throughout the world. In so doing they will provide major assistance for the preservation of biodiversity. 102 We would do well to recall the words of the Reverend Robert Malthus of Jesus College, Cambridge, who 200 years ago predicted that human population growth would outstrip our capacity to produce food. Economists, politicians, farmers, consumers and conservationists must now work together using all available means, including biotechnology to deal simultaneously with the needs of a rapidly expanding world population while at the same time seeking to reverse large-scale environmental degradation.

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#### References

- UNEP (2002), 'Synthesis GEO-3. Global Environmental Outlook 3; past, present and future perspectives' (URL: http:// www.grida.no/geo/geo3/english/overview/ 001.htm).
- 2. FAOSTAT (2003), Food and Agriculture Organisation (FAO) agricultural database (URL: http://apps.fao.org/page/collections?subset=agriculture).
- 3. UNDP (2001), 'Human Development Report 2001. Making New Technologies Work for Human Development', Oxford University Press Inc., New York (http:// hdr.undp.org/reports/global/2001/en/).
- Pinstrup-Andersen, P., Pandya-Loch, R. and Rosegrant, M. W. (1999), 'World Food Projects, Critical Issues for the Early 21<sup>st</sup> Century', 2020 Food Policy Report, International Food Policy Research Institute, Washington, DC.
- Oerke, E. C. (2002), 'Crop losses due to pest in major crops', in 'CAB International Crop Protection Compendium 2002. Economic impact', CAB International, Wallingford.
- UNDP (2001), 'Partnerships to fight poverty', Annual Report 2001, United Nations Development Programme, New York.
- 7. IFPRI (2002), 'Reaching Sustainable Food Security for All by 2020: Getting the Priorities and Responsibilities Right', slideshow presentation, International Food Policy Research Institute, Washington, DC (URL: www.ifpri.org/2020/books/ actionppt/actionppt.pdf).
- WHO (1999), 'Making a difference', World Health Report 1999, WHO (URL: http:// www.who.int/whr2001/2001/archives/ 1999/en/).
- Rosegrant, M. W, Cai, X. and Cline, S. A. (2002), 'Global Water Outlook to 2025: Averting an impending crisis', IFPRI, Washington, DC.
- 10. Pew (2003), URL: http:// www.pewclimate.org/global-warming-indepth/environmental\_impacts/
- Heap, B. (2003), 'GM crops and the Third World', in Ford, B. J., Ed, 'GM Crops, the Scientists Speak', Rothay House, Cambridge, pp. 79–87.
- 12. Berry, C. (2003), 'Before Frankenstein', *Quart. J. Med.*, Vol. 96, pp. 779–780.

- Harlander, S. H. (2002), 'The evolution of modern agriculture and its future with biotechnology', *J. Amer. Coll. Nutr.*, Vol. 21(3), pp. 161–165.
- Oerke, E. C. and Dehne, H. W. (1997), 'Global crop production and the efficacy of crop protection. Current situation and future trends', Europ. J. Plant Pathol., Vol. 103, pp. 203–215.
- Pimentel, D. (2001), 'Pricing biodiversity and ecosystem services', *Bioscience*, Vol. 51, pp. 270–271.
- Pretty, J. (2003), 'Could GM Crops Bring Benefits for Developing Countries?', Briefing Note for the GM Science Review Panel.
- Prakash, C. S. (2001). 'The genetically modified crop debate in the context of agricultural evolution', *Plant Physiol.*, Vol. 126, pp. 8–15.
- Reiss, M. J. and Straughan, R. (2002), 'Improving Nature? The Science and Ethics of Genetic Engineering', Cambridge University Press, Cambridge.
- 19. James, C. (2002), 'Global Status of Commercialization Transgenic Crops: 2002', ISAAA briefs no. 27-2002 (URL: http:// www.isaaa.org/).
- Nuffield Council on Bioethics (2003), 'The use of genetically modified crops in developing countries. A follow-up Discussion Paper to the 1999 Report "Genetically modified crops: the ethical and social issues", Nuffield Council of Bioethics, London (URL: http://www.nuffieldbioethics.org).
- 21. ESTO (2003), 'Review of GMOs under research and development and in the pipeline in Europe prepared by Karine Lheureux, Monique Libeau-Dulos, Hans Nilsagard, Emilio Rodrigues Cerezo (JRC IPTS, EC), Klaus Menrad, Martina Menrad (Fraunhofer ISI, Germany), Daniel Vorgrimler (University of Stuttgard-Hohenheim)', European Science and Technology Observatory Joint Research Centre, European Commission (URL: http://esto.irc.es/detailshort.cfm?ID\_report=1091).
- 22. Betz, F., Hammond, B. and Fuchs, R. (2000), 'Safety and advantages of *Bacillus thuringiensis* protected plants to control insect pests', *Reg. Toxicol. Pharmacol.*, Vol. 32, pp. 156–173.
- Gianessi, L. P., Silvers, C. S., Sankula, S. and Carpenter, J. E. (2002), 'Plant biotechnology: Current and potential impact for improving pest management', in 'U.S. Agriculture', National Center for Food & Agriculture Policy (NCFAP), Washington, DC, pp. 1–75.
- 24. Gianessi, L. P. and Carpenter, J. E. (1999), 'Agricultural Biotechnology: Insect Control

- Benefits', National Center for Food and Agricultural Policy (NCFAP), Washington, DC.
- 25. Heimlich, R. E., Fernandez-Cornejo, J., McBride, W. et al. (2000), 'Genetically engineered crops: Has adoption reduced pesticide use?', Agricultural Outlook, August, pp. 13–17.
- Phipps, R. H. and Park, J. R. (2002), 'Environmental benefits of genetically modified crops: Global and European perspectives on their ability to reduce pesticide use', J. Anim. Feed Sci., Vol. 11, pp. 1–18.
- Fawcett, R. and Towery, D. (2002), 'Conservation tillage and plant biotechnology: How new technologies can improve the environment by reducing the need to plow', accessed 2003, Purdue University (URL: http:// www.ctic.purdue.edu?CTIC/CTIC.html).
- 28. Cotton Council (2003), National Cotton Council of America, accessed 2003, Cotton Council (URL: http://www.cotton.org/).
- Moellenbeck, D. J., Peters, M. L., Birg, J. W. et al. (2001) 'Insecticidal proteins from Bacillus thuringiensis protect corn from corn rootworms', Nat. Biotechnol., Vol. 19, pp. 668–672.
- 30. Alston, J., Hyde, J. and Marra, M. (2002), 'An *ex ante* analysis of the benefits from the adoption of Monsanto's corn rootworm resistant varietal technology – YieldGard<sup>®</sup> Rootworm', *Tech. Bull.*, No. 103, National Science Foundation Center for Integrated Pest Management, Raleigh, NC.
- Greenplate, J., Penn, S., Shappley, Z. et al. (2000), 'Bollgard II efficacy: Quantifications of total lepidopteran activity in a 2-gene product', Proceedings, Beltwide Cotton Conferences, Vol. 2, pp. 1039–1040.
- 32. Marchosky, R., Ellsworth, P., Moser, H. and Henneberry, T. (2001), 'Bollgard and Bollgard II. Efficacy in Near Isogenic Lines of DP50 Upland Cotton in Arizona', in '2001 Arizona Cotton Report', pp. 311–315 (URL: http://ag.arizona.edu/pubs/crops/az1224).
- 33. Moar, W., Voth, R. and Woods, M. (2002), 'Efficacy of August-planted Bollgard II vs. Bollgard I and conventional cotton in Alabama; The acid test', in 'Proceedings of the Beltwide Cotton Production Conference Part 3A – Jan. 8–12, 2002', Atlanta, pp. 1–8.
- 34. Murphy, D. J. (1996), 'Engineering oil production in rapeseed and other oil crops', *Trends Biotechnol.*, Vol. 14, pp. 206–213.
- Vasil, I. K. (1996), 'Phosphinothricinresistant crops', in Duke, S. O., Ed, 'Herbicide-Resistant Crops', CRC Press, Inc., Boca Raton, FL, pp. 85–91.
- 36. Stalker, D. M., Kiser, J. A., Baldwin, G.,

- Coulombe, B. and Houck, C. M. (1996), 'Cotton weed control using the BXN system', in Duke, S. O., Ed, 'Herbicideresistant Crops: Agricultural, Environmental, Economic, Regulatory, and Technical Aspects', CRC Press, Inc., Boca Raton, FL, pp. 93–106.
- 37. Padgette, S., Re, D., Barry, G. et al. (1996), 'New weed control opportunities: Development of soybeans with a Roundup ready gene', in Duke, S. O., Ed, 'Herbicide resistant Crops: Agricultural, Economic, Regulatory and Technical Aspects', CRC Press, Inc., Boca Raton, FL, pp. 53–84.
- 38. Kaniewski, W., Maingi, D., Kaniewska, M. et al. (2000), 'Engineered resistance to sweetpotato feathery mottle virus in sweetpotato', in 'Fifth Triennial Congress of the African Potato Association', Kampala, Uganda, p. 37.
- Qaim, M. (2001), 'A prospective evaluation of biotechnology in semi-subsistence agriculture', *Agr. Econ.*, Vol. 25, pp. 165–175.
- Gonsalves, D. (1998), 'Control of the papaya ringspot virus in papaya: A case study', *Annu. Rev. Phytopathol.*, Vol. 36, pp. 415–437.
- Cheikh, N., Miller, P. W. and Kishore, G. (2000), 'Role of biotechnology in crop productivity in a changing environment', in Reddy, K. R. and Hodges, H. F., Eds, 'Climate Change and Global Crop Productivity', CAP International, New York.
- Falk, M. C., Chassy, B. M., Harlander, S. K., Hoban, T. J. IV, McGloughlin, M. N. and Akhlaghi, A. R. (2002), 'Food biotechnology: Benefits and concerns. Life Sciences Research Office', *J. Nutr.*, Vol. 132, pp. 1384–1390.
- Gilmour, S. J., Sebolt, A. M., Salazar, M. P., Everard, J. D. and Thomashow, M. F. (2000), 'Overexpression of the *Arabidopsis* CBF3 transcriptional activator mimics multiple biochemical changes associated with cold acclimation', *Plant Physiol.*, Vol. 124, pp. 1854–1856.
- Thomashow, M. F. (2001), 'So what's new in the field of plant cold acclimation? Lots!', *Plant Physiol.*, Vol. 125, pp. 89–93.
- Alia, Hayashi, H., Sakamoto, A. and Murata, N. (1998), 'Enhancement of the tolerance of *Arabidopsis* to high temperatures by genetic engineering of the synthesis of glycinebetaine', *Plant J.*, Vol. 16, pp. 155–161.
- Kasuga, M., Liu, Q., Miura, S., Yamaguchi-Shinozaki, K. and Shinozaki, K. (1999),
   'Improving plant drought, salt, and freezing tolerance by gene transfer of a single stress inducible transcription factor', *Nature Biotechnol.*, Vol. 17, pp. 287–291.

- 47. Xu, D., Duan, X., Baiyang, W., Hong, B., Ho, H. T. and Wu, R. (1996), 'Expression of a late embryogenesis abundant protein gene, HVA1, from barley confers tolerance to water deficit and salt stress in transgenic rice', Plant Physiol., Vol. 110, pp. 249–257.
- Zhang, H. X. and Blumwald, E. (2001), 'Transgenic salt-tolerant tomato plants accumulate salt in foliage butnot in fruit', Nature Biotechnol., Vol. 19, pp. 765–768.
- Rauch, J. (2003), 'Will Frankenfood save the planet?', Atlantic Monthly, October, pp. 103–108.
- Tilman, D., Fargione, J., Wolff, B. et al. (2001), 'Forecasting agriculturally driven global environmental change', Science, Vol. 292, pp. 281–284.
- 51. Bruinsma, J., Ed (2003), 'World Agriculture: Towards 2015/2030, an FAO Perspective', Earthscan, London.
- 52. Balmford, A. and Long, A. (1994), 'Avian endemism and forest loss', *Nature*, Vol. 372, p. 623.
- Jepson, P., Jarvie, J. K., MacKinnon, K. and Monk, K. A. (2001), *Science*, Vol. 292, p. 859.
- 54. BirdLife International (2000), 'Threatened Birds of the World', Lynx Edecions/BirdLife International, Barcelona/Cambridge.
- 55. Fairweather-Tait, S. (2003), 'Why the UK needs a nutrition strategy', Science and Public Affairs, September, The British Association for the Advancement of Science, Norwich.
- EU COM (2003), 424 Final 2003/0165
   (COD) Proposal for a Regulation of the European Parliament and of the Council on nutrition and health claims made on foods.
- 57. PASSCLAIM (2003), 'Process for the Assessment of Scientific Support for Claims on Foods, Phase One, Preparing the Way. A European Commission Concerted Action Project Coordinated by ILSI Europe', Europ. J. Nutr., Vol. 42, Suppl. 1, March.
- 58. FAO/WHO (2003), 'Report of the Joint WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Diseases (WHO TRS 916)', WHO, Geneva, 28 January to 1 February 2002.
- ILSI Europe (2001), 'Genetic Modification Technology and Food. Consumer Health and Safety', Concise Monograph, ILSI, Brussels.
- Fuchs, R. (2002), 'Foods derived from genetically modified crop plants', in Kotsonis, F. and Mackey, M., Eds, 'Nutritional Toxicology', 2nd edn, Taylor & Francis, Hampshire, Chapter 4, pp. 75–92.
- 61. Rabjohn, P., West, C. M., Connaughton, C. et al. (2002), 'Modification of peanut allergen Ara h3: Effects on IgE binding and T cell stimulation', Int. Archives Allergy Immunol., Vol. 128, pp. 15–23.

- 62. Kleiner, K. (2002), 'Engineering safer soya', New Scientist, Vol. 175(2360), p. 7.
- Tada, Y., Nakase, M., Adachi, T. et al. (1996), 'Reduction of the 14–16 kDa allergenic proteins in transgenic rice plants by antisense gene', FEBS Lett., Vol. 391, pp. 341–345.
- Buchanan, B. B., Adamidi, C., Lozano, R. M. et al. (1997), 'Thioreduxin-linked mitigation of allergic responses to wheat', Proc. Natl Acad. Sci. USA, Vol. 94, pp. 5372–5377.
- 65. Budziszewski, G. J., Croft, K. P. C. and Hildebrand, D. F. (1996), 'Uses of biotechnology in modifying plant lipids', *Lipids*, Vol. 31, pp. 557–569.
- 66. Kinney, A. J. and Knowlton, S. (1998), 'Designer oils: The high oleic acid soybean', in Roller, S. and Harlander, S. Eds, 'Genetic Modification in the Food Industry', Blackie Academic, London, pp. 193–213.
- Liu, Q., Singh, S. and Green, A. (2002), 'High-oleic and high-stearic cottonseed oils: Nutritionally improved cooking oils developed using gene silencing', J. Amer. Coll. Nutr., Vol. 21, 3(S), pp. 205S–211S.
- 68. DuPont Agricultural Products (1996), 'Safety Assessment of High Oleic Acid Transgenic Soybeans', Notification Dossier 62 FR 9155-9156, Docket No. 96-098-1 (URL: http://www.epa.gov/fedrgstr/EPA-IMPACT/1997/February/Day-28/i5023.htm).
- Lönnerdal, B. (2002), 'Expression of human milk proteins in plants', J. Amer. Coll. Nutr., Vol. 21, 3(S), pp. 2185–221S.
- Falco, S., Guida, T., Locke, M. et al. (1995), 'Transgenic canola and soybean seeds with increased lysine', Bio/Technology, Vol. 13, pp. 577–582.
- O'Quinn, P. R., Nelssen, J. L., Goodbank, R. D. et al. (2000), 'Nutritional value of a genetically improved high-lysine, high oil corn for young pigs', J. Anim. Sci., Vol. 78, pp. 2144–2149.
- Day, P. R. (1996), 'Genetic modification of proteins in food', Crit. Rev. Food Sci. Nutr., Vol. pp. 49–67.
- 73. Ye, X., Al-Babili, S., Klito, A. et al. (2000), 'Engineering the provitamin A (beta-carotene) biosynthetic pathway into (carotenoid-free) rice endosperm', *Science*, Vol. 287, pp. 303–305.
- Potrykus, I. (2001), 'Golden Rice and beyond', *Plant Physiol.*, Vol. 125, pp. 1157–1161.
- Shewmaker, C., Sheehy, J. A., Daley, M., Colburn, S. and Ke, D. Y. (1999), 'Seed-specific overexpression of phytoene synthase: Increase in carotenoids and other metabolic effects', *Plant J.*, Vol. 20(4), pp. 401–412.

- Mackey, M. (2002), 'The application of biotechnology to nutrition: An overview', J. Amer. Coll. Nutr., Vol. 21, 3(S), pp. 157S– 160S
- Rocheford, T. R., Wong, J. C., Egesel, C. O. and Lambert, R. J. (2002), 'Enhancement of vitamin E levels in corn', *J. Amer. Coll. Nutr.*, Vol. 21, 3(S), pp. 1995–204S.
- Shintani, D. and DellaPenna, D. (1998),
   'Elevating the vitamin E content of plants through metabolic engineering', *Science*, Vol. 282, pp. 2098–2100.
- 79. Lucca, P., Hurrell, R. and Potrykus, I. (2002), 'Fighting iron deficiency anemia with iron-rice rice', *J. Amer. Coll. Nutr.*, Vol. 21, 3(S), pp. 184S–190S.
- Grusak, M. (2002), 'Enhancing mineral content in plant food products', J. Amer. Coll. Nutr., Vol. 21, 3(S), pp. 1785–183S.
- 81. Persley, G. J. (2000), 'Agricultural Biotechnology and the Poor', Promethean Science Consultative Group on International Agricultural Research, Washington, DC.
- Phipps, R. H. and Cockburn, A. (2003), 'GM Technology: A Tool to Benefit Livestock Production', British Society of Animal Science, Nottingham University Press, Nottingham (URL: http:// www.bsas.org.uk/meetings/annlproc/ pdf2003/210.pdf).
- Gardiner, P. and Devendra, C. (1995),
   'Global Agenda for Livestock Research',
   Proceedings of a Consultation, ILRI,
   Nairobi, Kenya, 18th–20th January, 1995.
- 84. Tilman, D. (1999), 'The ecological consequences of changes in biodiversity: A search for general principles', *Ecology*, Vol. 80(5), pp. 1455–1474.
- Kalscheur, K. F., Teter, B. B., Piperova, L. S. and Erdman, R. A. (1997), 'Effect of fat source on duodenal flow of *trans*-C18:1 fatty acids and milk fat production in dairy cows', *J. Dairy Sci.*, Vol. 80, pp. 2115–2126.
- 86. Payne, J. H. (1977), 'DuPont petition 97–008–01p for determination of nonregulated status for transgenic high oleic acid soybean sublines G94–1, G94–19 and G–168:
  Environmental assessment and finding of no significant impact', US Department of Agriculture, Animal and Plant Health Inspection Service, Biotechnology and Scientific Services, Riverdale, MD.
- 87. Wehrspann, J. (1998), 'New traits of seed buying', Farm Industry News, Vol. 31(10).
- 88. Smart, V., Foster, P. S., Rothenberg, M. E., Higgins, T. J. V. and Hogan, S. P. (2003), 'A plant-based allergy vaccine suppresses experimental asthma via an IFN-γ and CD4+CD45RB<sup>low</sup> T cell-dependent mechanism', J. Immunol., pp. 2116–2126.

- 89. Streatfield, S. J., Jilka, J. M., Hood, E. E. et al. (2001), 'Plant-based vaccines: Unique advantages', Vaccine, Vol. 19, pp. 2742–2748.
- Tacket, C. O., Mason, H. S., Losonsky, G. et al. (2000), 'Human immune responses to a novel Norwalk virus vaccine delivered in transgenic potatoes', J. Infect. Dis., Vol. 182, pp. 302–305.
- 91. Arawaka, T., Chong, D. K. X. and Langridge, W. H. R. (1998), 'Efficacy of a food plant-based oral cholera toxin B subunit vaccine', *Nature Biotechnol.*, Vol. 16, pp. 292–297.
- 92. Richter, L. J., Thanavala, Y., Arntzen, C. J. and Mason, H. S. (2000), 'Production of Hepatitis B surface antigen in transgenic plants for oral immunization', *Nature Biotechnol.*, Vol. 18, pp. 302–305.
- Ma, J. K. and Hein, M. B. (1995), 'Therapeutic potential of antibodies produced in plants', *Trends Biotechnol.*, Vol. 13, pp. 522–527.
- Moffatt, A. S. (1999), 'Engineering plants to cope with metals', *Science*, Vol. 285(5426), pp. 369–370.
- Mejare, M. and Bulow, L. (2001), 'Metalbinding proteins and peptides in bioremediation and phytoremediation of heavy metals', *Trends Biotechnol.*, Vol. 19(2), pp. 67–73.
- Hirsch, K. D., Korenkov, V. D., Wilganowski, N. L. and Wagner, G. J. (2000), 'Expression of *Arabidopsis* CAX2 in tobacco. Altered metal accumulation and increased manganese tolerance', *Plant Physiol.*, Vol. 124(1), pp. 125–133.

- Zhy, Y. L., Pilon-Smits, E. A., Tarun, A. S. et al. (1999), 'Cadmium tolerance and accumulation in Indian mustard is enhanced by over expressing gamma-glutamylcysteine synthetase', *Plant Physiol.*, Vol. 121(4), pp. 1169–1178.
- 98. Commission of the European Communities (2001), 'Proposal for a Directive of the European Parliament and of the Council on the promotion of the use of biofuels for Transport', 7th November, COM(2001) 547.
- 99. Firbank, L. G., Perry, J. N., Squire, G. R. et al. (2003), 'The implications of springsown genetically modified herbicide-tolerant crops for farmland biodiversity: A commentary on the Farm Scale Evaluations of Spring Sown Crops', London (URL: http://www.defra.gov.uk/environment/fse/index.htm).
- 100. Dale, P. (2003), 'Submission to ACRE Secretariat. The Farm Scale Evaluations of herbicide tolerant GM Crops', November, Norwich (URL: http:// www.livegroup.co.uk/ acrefarmscaleevaluations/SSL/files/ Philip%20J%20Dale%20 Evidence%20101103.pdf).
- Coghlan, A. (2003), 'GM sugar beet "far more environmentally friendly" ', New Scientist, 6th December, p. 17.
- 102. Raven, P. (2003), 'The Ecology of Agriculture', presentation at the Natural History Museum, Darwin Centre, London, 22nd May.