INSIDE THE HOTHOUSES OF INDUSTRY

Feeding the world is going to require the scientific and financial muscle of agricultural biotechnology companies. **Natasha Gilbert** asks whether they're up to the task.

Wheat growing in one of Monsanto's growth chambers.

N. GILBERT

Do Not Water, says the small notice by the pots of withered, brown maize seedlings, the genetically unlucky ones in an experiment testing maize's tolerance to drought. Five minutes after stepping into the huge greenhouse in which these plants are attempting to grow at the research headquarters of Monsanto in St Louis, Missouri, I am beginning to feel genetically disadvantaged too. Sweat is beading on my skin. Like the desiccated plants, I am clearly not cut out for the fierce summer temperatures that the greenhouse's climate is set to imitate. Just next to them though, a row of green, sprightly seedlings is faring better thanks to a gene that researchers inserted from the bacterium *Bacillus subtilis*. Just as lively is Dianah Majee, the plant biologist showing me around. Her face hasn't even worked up a shine.

These green plants and the scientists that produced them are unusual in ways not visible to the eye. They are Monsanto's entry in a race to make the first transgenic, drought-tolerant maize (corn) that is commercially available to farmers. The race is tight. But after more than 20 years of research and development (R&D), Monsanto says it is now two years away from launching the seeds onto the market. And within the next few years, the company and its major competitors hope to bring to market other transgenic crops, resistant to stresses such as soils starved of nitrogen, phosphorus and other essential nutrients.

Maize containing a drought-resistant bacterial gene is put to the test at Monsanto.

N. GILBERT

In pursuing these crops, Monsanto and the other giants of agricultural biotechnology are making a significant departure from what until now has been a mainstay of their business: developing and selling pesticide- or herbicide-resistance crops, such as Monsanto's *Bt* maize. When these plants were first introduced in the 1990s they produced dramatic increases in yield for farmers — and a windfall in profits for the companies supplying the seed. But the yields have peaked, and so have the profits. Now the next big commercial gains lie in crops that can withstand water- and nutrient-deficient soils. US farmers lose on average 10–15% of their annual yield because of drought and water stress.

Crops that can beat these stresses are also a vital part of the solution to the global food crisis. If the 9 billion people expected to inhabit the world by 2050 are to be fed, then farms in low-income countries must grow more food, sustainably, on water- and nutrient-poor soils (see page 546). Researchers and policy-makers realize that they can't meet the food-security challenge without the private sector, which makes up a significant share of the global agricultural research effort (see 'Public vs private'). Monsanto's annual research budget alone is US$1.2 billion, just topping the US federal government's total spend on agricultural science of $1.1 billion in 2007 (the most recent figures available). In contrast, the Consultative Group on International Agricultural Research (CGIAR), the world-leading group of centres carrying out agricultural R&D for developing countries, has an annual budget of $500 million.

Getting together

So in their demand for hardier crops, the commercial aims of the biotechnology companies and the requirements of the developing world have aligned — and companies such as Monsanto hope to fulfil them. In June 2008, Monsanto pledged to double yields in its core crops of maize, soya bean and cotton by 2030 over 2000 levels. In September of the same year, Monsanto's chairman promised to "improve the lives of an additional 5 million resource-poor farmers", in large part by making some of its seed technology available to increase their productivity. Other companies have made similar pledges.

All this leads to another reason why the green, transgenic seedlings in the stifling Missouri greenhouse stand out. In 2008, Monsanto partnered with the African Agricultural Technology Foundation, a non-profit research organization in Nairobi, Kenya, to apply the techniques and discoveries it has made with its commercial drought-tolerant maize to developing drought-tolerant varieties for subsistence farmers in sub-Saharan Africa, to be available as quickly as possible after commercialization in the United States. The partnership, which is also funded with $47 million in grants from the Bill & Melinda Gates Foundation in Seattle, Washington, and the Howard G. Buffett Foundation in Decatur, Illinois, is one of a handful of exceptionally large projects established in recent years in which public and private sectors have joined forces to tackle food scarcity in developing countries. The companies say that these investments are just good business sense because they will create future customers as developing-world farmers gradually move from subsistence to profits, making money to spend on seed. The companies also see an opportunity to buff their corporate images with a humanitarian cloth.

Slow progress

It will take more than buffing to overcome critics' deep scepticism about commercial biotechnology. Genetically modified (GM) crops, they say, have so far done little for the developing world. Earlier humanitarian initiatives have yet to reach fruition. Golden rice, for example — transgenic rice designed to combat vitamin A malnutrition — has been in development since 1990 (see page 561). Critics ask what has taken so long; they worry that industry's grasp on intellectual property is holding up research progress; they question why these supposedly transformative transgenic technologies have yet to put food in the hungriest bellies. "I don't think the private sector is doing enough," says Achim Dobermann, deputy director general for research at CGIAR's International Rice Research Institute (IRRI) in Manila, the Philippines.

Roger Beachy, director of the US Department of Agriculture's National Institute of Food and Agriculture in Washington DC, wonders how far the agricultural biotech companies are willing to go. "Have they made as much progress in developing countries as they should have?" he asks. "What do they see as their responsibility in the developing world?" To many scientists, the answers to these questions are hidden behind a corporate facade.

Which is why I'm here, slowly wilting in Monsanto's greenhouse, and why I travelled to two other giants in the sector — Pioneer Hi-Bred in neighbouring Iowa, and the UK research headquarters of Swiss company Syngenta — to tour their labs, greenhouses and test fields, where the next generation of crops are sprouting. I wanted to see them and talk to senior researchers and executives about the future of their science, their business — and, inextricably, the future of the planet's food.

I sit in the small waiting room of Monsanto's main building, A, with its single bench and friendly security guard. Buildings B through to Z are scattered around the manicured gardens and endless car parks that make up the rest of its headquarters. Monsanto employs around 5,000 scientists and technical assistants worldwide and splits its R&D budget equally between biotechnology and traditional plant breeding. (Monsanto, like the other companies I visited, does not break down how much of the budget is spent on its humanitarian projects.)

"The idea that these farmers get free handouts forever is not sustainable."

For its GM crop work, Monsanto's scientists screen hundreds or even thousands of genes from plants, bacteria and other organisms for ones that might endow plants with a desired trait. The drought-tolerant *B. subtilis* gene, *cspB*, that they found helps bacteria deal with environmental stress such as cold temperature. When inserted into maize plants it helps them cope with drought by disentangling RNA, which folds up abnormally when the plant is water-starved. The theory is that the energy the plant would have spent fixing drought-entangled RNA can now be sunk into grain.

Away from the sweltering greenhouses, posters provide a regular reminder of Monsanto's 'pledge' to the world in six different languages. The company promises dialogue, transparency, respect, sharing and benefits. And Bob Reiter, vice-president for breeding technologies at Monsanto, is up front about the company's business-minded approach to its humanitarian work. Crops that will make the company money in the short term, in richer countries, could also eventually make money in lower income ones. "The initial approach is to help the subsistence farmer get on his feet," he says. "There has to be a humanitarian element to it. But you have to think about what a viable agricultural industry in Africa looks like, and the idea that these farmers get free handouts forever is not sustainable."

Long-term plan

It is with these sentiments that Monsanto entered into its public–private partnership with the African Agricultural Technology Foundation. It is not giving away the green strain that I saw thriving in the greenhouses. It is giving away the resources it used to make it — such as the sequence of the *cspB* gene, plus information about other drought-tolerant genes and traits that the researchers are introducing into maize through traditional breeding. Crops developed through the partnership will be made available royalty free to subsistence farmers. If a country moves from subsistence farming to commercial farming then, in theory, the company could start charging for the seed.

But first Monsanto has to get its 'first generation' drought-tolerant maize into fields in the developed world. The

T. KARUMBA/AFP/GETTY IMAGES

Dying from drought: as part of public-private partnerships, biotech firms are developing crops that can withstand drought and poor soils.

company has finished testing the seed; now it has to secure regulatory approval from US federal agencies and scale up seed manufacture. Researchers at Monsanto are already working on 'second generation' crops — the details of which the company is keeping close to its chest — that can grow in a wider range of environments across the United States. Behind the rows of silver doors to the company's 108 growth chambers, an even hardier strain of maize is surely growing.

Mechanized engineering

One state north of Missouri, on the outskirts of the small midwestern town of Johnston, Iowa, the last few rows of houses suddenly drop away and a sea of young green maize rolls up to the horizon. In patches the maize has turned yellow and its growth is stunted. Recent intense rainstorms have flooded parts of the fields, washing nutrients from the soil that are vital to the crop's healthy growth, including nitrogen fertilizers.

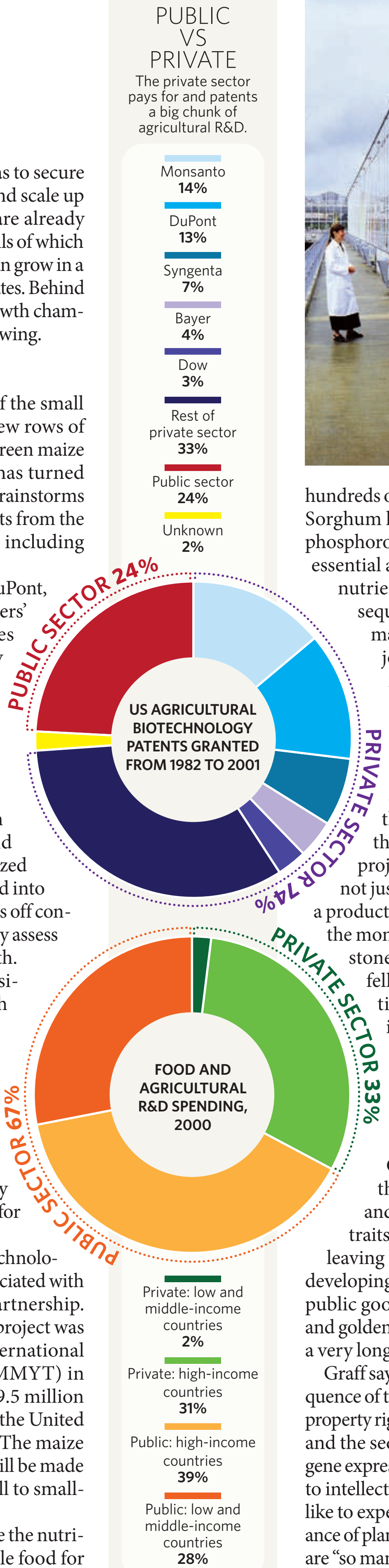
Pioneer Hi-Bred, part of the chemical giant DuPont, saw an opportunity here to increase its customers' yields. When global nitrogen fertilizer prices peaked in 2008 at more than $450 a tonne, nearly double the previous year's cost, the company ramped up a research project that it had begun in 2005 to develop maize hybrids that produce the same yield on less fertilizer.

Pioneer isn't quite the biotech behemoth that Monsanto is: in 2009 DuPont spent $734 million on its agriculture and nutrition R&D, which includes Pioneer Hi-Bred's work on seeds and crop protection. The company has now mechanized much of the process of linking the genes inserted into plants to desired traits. A robot hauls maize plants off conveyor belts; another takes digital images to rapidly assess how novel genes have changed the plants' growth.

In Pioneer's case, researchers hit on one possible gene in the red alga *Porphyra perforata*, which can grow in environments with nitrogen levels 100 times lower than maize. The gene codes for the enzyme nitrate reductase, which converts nitrate into nitrite. "We don't really know how it works," says Dale Loussaert, a senior scientist working on the project, of the algal gene. Even so, he says, "the plant models in the lab look promising. The yields look good." The company does not expect to have a product on the market for another 10–12 years though.

Pioneer has agreed to donate the transgenic technologies, molecular markers and other resources associated with its nitrogen-use project to a public–private partnership. The Improved Maize for African Soils (IMAS) project was launched in February 2010. It is led by the International Maize and Wheat Improvement Centre (CIMMYT) in Mexico, part of the CGIAR, and it received $19.5 million from the Bill & Melinda Gates Foundation and the United States Agency for International Development. The maize varieties that will be developed through IMAS will be made available royalty free to seed companies that sell to small-scale farmers in sub-Saharan Africa.

Pioneer is also involved in a project to increase the nutritional content of sorghum, a crop that is a staple food for



SOURCE: G.D. GRAFF *ET AL. NATURE BIOTECHNOL.* **21**, 989–995 (2003)

SOURCE: P. G. PARDEY & P. L. PINGALI *REASSESSING INTERNATIONAL AGRICULTURAL RESEARCH FOR FOOD AND AGRICULTURE* (GCARD, 2010)

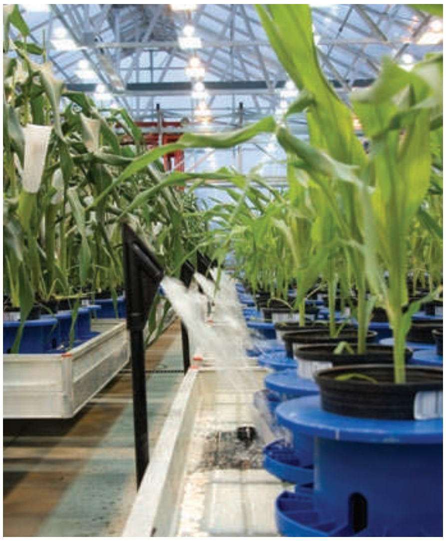
SYNGENTA

hundreds of millions of people throughout Africa and Asia. Sorghum has high levels of phytate — the form in which phosphorous is stored in plants — which binds strongly to essential amino acids, vitamin A, iron and zinc, so these nutrients are not available in a digestible form. Consequently, people who depend on sorghum as their main food source are often malnourished. Since it joined in 2005, the company has donated technologies worth $4.8 million to the scheme, led by Africa Harvest, a non-profit foundation based in Nairobi, Kenya.

Florence Wambugu, founder and chief executive of Africa Harvest, used to sit on a science advisory panel for DuPont, and so knew that the company was developing technologies that would be useful to Africa Harvest's sorghum project. She approached the company for help. "It is not just the technology donation; this won't amount to a product. We had to get outside expertise to help manage the money and people, and ensure we are meeting milestones," she says. Marc Albertsen, a senior research fellow at Pioneer Hi-Bred and co-principal investigator on the sorghum project, says that tests in June showed that transgenic sorghum varieties developed by Pioneer produced 80% less phytate but 20% more iron and 30% more zinc than conventional varieties.

Such results are not going to assuage the critics. Gregory Graff, an agricultural economist at Colorado State University in Fort Collins, says that the majority of companies' R&D spending and effort still goes towards blockbuster crops with traits, such as pest control, that benefit agribusiness, leaving neglected many crops that are important in the developing world. "They bring out one or two examples of public good research, such as drought-resistant varieties and golden rice, but research on these has been going on for a very long time and none are actually ready yet," he says.

Graff says that the lack of progress is in large part a consequence of the hold that the private sector has on intellectual-property rights to crucial technology, such as genetic markers, and the sequences of key genes and 'promoters' that drive gene expression. Dobermann, of the IRRI, agrees that access to intellectual property is a problem. His institution would like to experiment with traits to improve the drought tolerance of plants and their efficiency in using nitrogen, but there are "so many restrictions" on the use of patented technology

PIONEER

Syngenta's research greenhouses (left), and some of Pioneer Hi-Bred's experimental maize.

that researchers at his institute concluded "it was not worth getting into," he says. "We either have to reinvent the technology ourselves or use a second-class solution," he says.

John Bedbrook, vice-president of agricultural biotechnology at DuPont, agrees that "tensions" over access to intellectual property exist, but says the company has to remain "dispassionate". Without intellectual property, he says, companies would have little incentive to invest in the research to begin with. But, he adds, companies could be "more open source with enabling technologies" such as promoters. Reiter says that restrictions on access to intellectual property are often misconceived. When public researchers ask the company for access to patented technology, he says, it often turns out that the subject of their research was not actually covered by a patent. All this leaves a question: what has really been holding up these projects?

The real delays

This was the issue that I discussed at Syngenta, whose modern UK research headquarters sit in 260 hectares of verdant English farmland near Bracknell. Syngenta has a history in public–private partnerships through the golden rice project, which AstraZeneca (the agribusiness part of which became Syngenta) joined in 2001. Syngenta worked to increase the amount of a precursor of vitamin A in the rice and make seeds available royalty free to subsistence farmers in sub-Saharan Africa, but the company retains commercial rights elsewhere. (The IRRI, part of the Golden Rice Humanitarian Board, which now directs the project, expects to introduce seeds to farmers by 2012.) But some critics view golden rice as an agonizing failure because it has taken so long, and have been highly distrustful of the company's involvement, assuming that the project was mired because of the numerous patents involved.

Not true, says Ingo Potrykus, chairman of the Golden Rice Humanitarian Board and, as an academic researcher, one of the inventors of golden rice. He says that the team initially thought that they had to obtain free licences for 70 patents protecting technologies used in the rice development. But when Syngenta joined the project, its lawyers found that only a handful of these patents applied to the countries where golden rice was targeted. So in fact, he says, intellectual property has not been a major problem. "Without the cooperation of the private sector we would probably never have been able to solve the intellectual-property mess and the project would have ended at this stage," says Potrykus.

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Mike Bushell, Syngenta's chief scientist, says complex technology and regulations are the real hold-ups for transgenic crops. "R&D takes around 10 years and then you have to go through the regulatory stage," he says. Bushell says critics overlook how long it takes to develop crop varieties with complex traits such as drought tolerance, which involve many genes and are greatly influenced by environmental conditions. And passing regulatory hurdles involves reams of tests showing, for example, that a gene is stably and safely expressed.

As we stroll past Syngenta's 'monsoon machine', which recreates harsh weather conditions, the discussion turns to the volatile topic of GM crops and their regulation. In 2004–05, the company moved the bulk of its GM research out of Europe and to the United States, in part because of Europe's difficult climate for GM research and the nonexistent market. But this year has seen some signs that the continent's strict stance on GM crops is softening (see D. Butler *Nature* doi:10.1038/news.2010.112; 2010). That could be good news for the developing world, Bushell says. Although he acknowledges that transgenic crops are not the only solution to increased food production, particularly in the developing world, he argues that they are an important component in a tool box that also includes improved agronomic practices and traditional breeding methods.

Nicholas Kalaitzandonakes, an agricultural economist at the University of Missouri-Columbia who tracks the agricultural biotech industry, says that the industry is making a substantial investment in these public–private partnerships. "I have the impression that people in the industry know they can't make money on [these products] in developing countries but they honestly want to make it available. But they also want to watch their backs." If something goes wrong — for example the research fails, the partnership breaks down, or a transgene contaminates local commercial supplies — a company could face heavy financial liability and public relations fall-out, Kalaitzandonakes says. "It's not a simple thing to manage risk and potential risk."

This cautiousness is partly why only a handful of these partnerships exist. Yet Kalaitzandonakes is optimistic that once one product comes on the market — be it golden rice, a drought-tolerant maize or a biofortified sorghum — then businesses, governments and the public will become more confident in backing the next. The optimism is tangible at Syngenta too. Earlier this year the company started a project with the CIMMYT to research and develop more productive wheat varieties for farmers in the developing world. Bushell says that the company has learnt a lot from its involvement in helping to develop golden rice.

Outside, fields of winter wheat are bordered by an unruly metre-wide strip of wild grasses and flowers designed to attract bees and other pollinating insects. This farming practice, which Syngenta is hoping to encourage across Europe, is also part of the company's efforts to make agriculture sustainable. The world's future food depends not just on crops, however cleverly they are engineered — the ecosystems to support them must have a future too. ■

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See Editorial, page 531, and food special at www.nature.com/food.