The Genomic Revolution: Everything You Wanted to Know About Plant Genetic Engineering But Were Afraid to Ask

Roger N. Beachy, Daphne Preuss, and Dean Dellapenna

Moderator: ***Robert Haselkorn***

The Academy's Midwest Center hosted the 1849th Stated Meeting on October 27, 2001, at the Peggy Notebaert Nature Museum of the Chicago Academy of Sciences. Fellows and their guests were given a private tour of the museum, including its nationally acclaimed Butterfly Haven.

The Stated Meeting featured a discussion on the genetic modification of plants, moderated by Robert Haselkorn, Fanny L. Pritzker Distinguished Service Professor at the University of Chicago. The panelists were Roger N. Beachy, director of the Donald Danforth Plant Science Center (St. Louis); Daphne Preuss, professor of molecular genetics and cell biology, University of Chicago and Howard Hughes Medical Institute; and Dean DellaPenna, associate professor of biochemistry and molecular biology, Michigan State University.

Roger N. Beachy

Agricultural biotechnology had its start in the early 1980s, at about the same time that pharmaceutical biotechnology was producing insulin, human growth hormones, and other pharmaceuticals in bacteria. The first genetic engineering of plant cells and the development of transgenic plants took place in 1983 in St. Louis at Washington University and at the Monsanto Company. At about the same time, laboratory workers in Belgium and Germany also developed genetically engineered plants.

Left to right: Speakers Dean DellaPenna (Michigan State University), Robert Haselkorn (University of Chicago; moderator), Daphne Preuss (University of Chicago), and Roger N. Beachy (Donald Danforth Plant Science Center).

By 1986, federal regulatory agencies, including the US Department of Agriculture and the Food and Drug Administration (joined later by the Environmental Protection Agency), were beginning to evaluate transgenic plants for their safety as food and as agricultural products (e.g., animal feed), as well as for their safety in the environment. By 1996, the first genetically engineered plants were sold commercially. While genetic engineering was a new technology in the 1980s, biotechnology, which involves the planned use of living systems to make new products, is an old science. Wine and bread are the products of biotechnology. But what made the new biotechnology different from the old was the ability to introduce novel or foreign genes into plants.

As biotechnology progressed—from the bacterial production of insulin and growth hormones, to yeast strains that could make new products, to plants that could have new traits—the science undergirding biotechnology moved rapidly, leading to discoveries that would ultimately lead to new products.

What genes were scientists introducing into transgenic plants? A major goal in my laboratory was to modify plants genetically so that they would resist infection by plant viruses. Other researchers were developing plants that could resist insect attack. Both groups had the same goal: to develop plants that eliminate or reduce the need for chemical insecticides.

Viruses are transmitted by several types of insects, such as aphids and white flies, and farmers control the viruses by controlling the insects with insecticides.

I naively thought that developing virus-resistant plants in order to reduce the use of insecticides would be viewed as a positive advance. However, the Environmental Protection Agency (EPA) basically said, "If you use a gene that protects the plant from a virus, which is a pest, that gene must be treated as a pesticide." Thus, the EPA considered the genetically transformed plants to be pesticidal. The point of this story is that as genetic sciences and biotechnology developed, the federal regulatory agencies were taken somewhat by surprise. The agencies did not have the background or expertise to regulate the new varieties of crop plants that were being developed, and they did not have the background to regulate the environmental impacts of transgenic crops in agriculture. Those in the environmentalist community, as well as those who were against the use of genetic technologies per se, raised the concern that no one was "protecting the store" and advocated that the technology should be blocked from moving ahead. On one side are those who say that the new technology can reduce the use of insecticides, save soil runoff, reduce the cost of agricultural production, and be of broad benefit to society. On the other side are those who say that the crops should be tested for a longer time before being grown commercially.

Agricultural biotechnology has proven very successful to date. Since 1996, when the first genetically modified cotton, corn, and soybeans with resistance to certain types of insects or to certain herbicides were introduced, there has not been a single incidence of illness related to foods, feeds, or fibers developed from these crops. Furthermore, it is estimated that since 1996, the use of insect-resistant crops has resulted in a decrease in the use of insecticides, amounting to more than two million gallons per year.

One of my interests has been making available to scientists in developing countries the science and the intellectual property associated with biotechnology, for use in solving local problems. Biotechnology is a science of rich countries; it is high-end science. The low-cost, pre-1980s agricultural science of plant breeding is still effective, but not as effective as some of the more modern biotechnologies. Many of us are concerned that intellectual property laws will restrict the benefits of biotechnology to use in developed countries. It is my opinion that both universities and private companies are responsible for this situation. A key issue is what we in academia do to make biotechnology available for use in developing countries. How do we provide the training necessary to enable local scientists to conduct work with cassava, yams, cowpeas, and chickpeas that is similar to what has been done to advance production of corn, cotton, and soybeans? In many parts of the world, small-holder farmers and, most important, different crops face different challenges and require different solutions than those required for corn, cotton, and soybeans.

The following is an example of how biotechnology can serve developing nations. When the Monsanto Company applied genetic transformation to cotton to protect it from cotton boll worm (a serious pest worldwide), they used a gene from a soil bacterium, *Bacillus thuringiensis.* This bacterium has been used by organic farmers for more than thirty years to control insects in home gardens.

Scientists learned which protein in the bacterium controls insect larvae. By inserting the gene that codes for this insecticidal protein into cotton, they produced new varieties that require fewer insecticide applications than do others. The use of insect-resistant varieties of cotton saves several million pounds of chemical insecticides annually. Opponents of biotechnology predicted that only the big farmers would benefit from the new, more costly varieties of cotton. In fact, however, the opposite is true. Small-holder farmers in China and in South Africa saw their profits increase by an average of $150 to $200 per hectare per year by using the new varieties of insect-resistant crops. The farmers paid more for the seeds, but they did not have to buy the chemicals that they normally would have sprayed on the crops.

Left to right: New Fellows Don Michael Randel, Robert Rosner, Douglas Diamond (all, University of Chicago), and Guy Bush (Michigan State) in the Butterfly Haven of the Peggy Notebaert Nature Museum, Chicago.

In summary, agricultural biotechnology can be successfully used to develop genetically modified crops that are protected against pests and pathogens. In later remarks by Dean DellaPenna, you will hear that biotechnology can also be used to increase the quality and quantity of nutrients in foods. These types of breakthrough discoveries can play a significant role in alleviating food shortages around the world.

An economist or sociologist might insist that adequate transportation, electricity, education, women's rights, and welfare are equally important factors in advancing underdeveloped nations. No one is naive enough to think they have the singular answer; progress can be made only if all aspects of a problem are addressed. It is our moral responsibility to improve the living conditions of those around the world however we can. We need to face the many societal and economic challenges that have become increasingly apparent during the past several years. Some of those challenges will involve applications of biotechnologies in food and agriculture that complement medical biotechnology. These *will* be part of the solution.

Daphne Preuss

The truth is that a lot of the food you've been eating over the years has been genetically modified, via either classical plant breeding or more modern genetic transformation. For example, about 70 percent of the soybean crop and more than half of the corn in this country are genetically transformed; people have been consuming them for a number of years with no real illnesses and no problems. What we don't often think about is that we are at the current point in a continuum of work that has been going on for a very long time. Those of us who own dogs or cats know that our favorite animals look nothing like the wild organisms they're descended from, including coyotes, wolves, and dingoes. We have poodles, Great Danes, and dalmatians, and those arose because about 10,000 years ago, people started breeding them. We're not so aware that the same thing has been happening in agriculture. Over the last 10,000 years, humans have absolutely transformed all the food we eat. When you go into a grocery store, look in the produce section: there is very little that has not been genetically transformed by people. Other than maybe the really small wild blueberries and watercress, virtually everything else is the product of genetic manipulation by humans. Our food sources, therefore, are really not natural, and they haven't been for a very long time. The way the public uses the word *natural* is deceptive: we have this general idea that something natural is safe, harmless, and good, but nature is not always like that.

Often, when people did breeding in the conventional sense, the resulting plants were harmful. As a result, a regulatory system evolved to test crops that were bred and produced. That same system was employed when the more modern biotechnology methods were used to develop novel plants.

Let's discuss conventional breeding and how it works. When two plants are crossed, at least 25,000 genes from each parent are mixed in random combinations. Then the offspring are examined, and the desirable ones are chosen. Biotechnology has given us the opportunity to take one gene, put it in, and look at what happens, instead of doing a random kind of shuffling. It's much more precise, it's much more controlled, because you know exactly what you've done. Most researchers in plant biology think that this new way of developing new varieties is much more refined and much safer than conventional breeding.

Chromosomes—the DNA-containing bodies inside cells—are the vehicles that carry genes. In a genetically modified plant, a gene is taken from one source and put inside another chromosome that then carries that gene. Our group is interested in understanding how to build chromosomes from scratch.

Why do that? Until recently, most genetic engineering has been related to delivering one gene at a time, but now we're trying to build entire chromosomes that will be delivered to the plants, adding sets of genes. We look at plants as potential factories that can make all kinds of chemicals, including pharmaceuticals. If you have flexibility in the ability to design a plant, you can get plants to make all kinds of compounds cheaply and easily. Farmers in developing countries can then grow these new crops and produce desirable chemicals without contaminating the environment with the byproducts of traditional chemical synthesis that takes place in factories. Plants are a convenient, safe, cheap, and easy means of making food, fiber, pharmaceuticals, and other valuable materials. The more tools we have to manipulate plants, the better. I think that biotechnology offers a huge amount of opportunity for the future if we can resolve the regulatory issues and make sure that plant transformation is done safely.

Dean DellaPenna

Two questions drive our laboratory: How are plant compounds made? What do they do in plants?

Plants are fantastically unique organisms. They're the basis of our food chain; everything that we eat is derived either directly or indirectly from plants. This means that plants have a profound impact on our nutrition, health, and well-being. Plant biologists look at nutritional components in plants very much as nutritional biologists do: we divide them into macronutrients, the major components of diet that are building blocks and energy resources, and micronutrients, which are divided into essential and nonessential micronutrients. The essential ones, listed on cereal boxes, include 13 vitamins and 17 minerals. The nonessential nutrients are phytochemicals that have profound effects on human physiology and can impact genetic predispositions to certain diseases.

Over the past 100 years, agriculture has done a wonderful job. In the 1800s predictions of population growth suggested a population crash due to food shortages that would have taken place by now. This has not happened because agriculture has been doubling, and then doubling again, the amount of food we can produce per acre. However, the modern food production system has caused an overreliance on just a few different crops. A few hundred years ago, the bulk of our diet came from 20 to 30 different crops; now, over half of our diet comes from just three: rice, wheat, and maize (corn). This has been necessary to feed the growing world population, but it has also inadvertently caused a loss of biochemical diversity in our diet, which brings some serious problems. Such problems are present in both the developing and the developed worlds.

For example, worldwide, 800 million people are chronically malnourished: that is, these people are deficient in both macronutrients and micronutrients. These are the poorest of the poor. In addition, three times that number—about two and a half billion people— are severely deficient in one or more micronutrients, even though they get adequate or marginally adequate macronutrients or calories every day. This "hidden hunger" affects cognitive and physical development and takes its largest toll on women and children. The people who are deficient in these nutrients often live on less than $2 a day. This means that they don't buy vitamins; the only way they get nutrients is through food. Moreover, in the 20 years between 2000 and 2020, most population growth will take place in developing countries where these problems exist.

Our country has nutritional problems as well. Certainly, our foods are fortified, and those who can afford to buy $5 boxes of cereal get reasonable amounts of vitamins and minerals. But sections of our population—most notably the elderly, the poor, and certain ethnic groups—don't get the nutrients they need; they could be helped by the manipulation and enhancement of nutrients in food. Our nation's other problem is diseases of overabundance: we're living a little too large. That is, we have increases in cancers, heart attacks, and other diseases related to extravagant lifestyles.

The good news is that many of these problems can be mitigated by diet. For example, the recommended dietary allowance for vitamin E, and the minimum amount needed to prevent deficiencies, is 22.5 international units (IU) daily—but higher levels in the diet often have beneficial effects (this is the case for other vitamins and minerals as well). For example, consumption of vitamin E at the level of 100 IU daily is correlated with a decrease in cardiovascular disease. In this country, an estimated 30 percent of Americans have low serum levels of vitamin E. Vitamin E is an antioxidant, and low levels of it during your lifetime increase the oxidative load on your body. Dying, in a biochemist's analysis, is simply a process of oxidizing and, eventually, giving up. Hence, antioxidants in our diet, like vitamin E, have a significant beneficial effect on our longevity. Low levels of antioxidants have been correlated with increased risk of heart attack, the number-one killer in this country. Increasing dietary levels of vitamin E could have a significant positive effect on the general population.

During the past 8 to 10 years, our lab has been tearing apart the pathway for vitamin E synthesis and trying to manipulate it in plants to encourage vitamin E synthesis. Most of our work has been done in the model organism *Arabidopsis,* a mustardlike plant, but I have extrapolated the results to soybean. Soybean makes up 80 percent of the vegetable oils in our diet, and vegetable oils are where we get most of our vitamin E. The wild type of soybean gives you about 12 IU, which is about half of the recommended daily allowance. With the introduction of the three genes that we now have in hand, we can enhance soybean vitamin E production to about 100 IU daily in the average American diet. This 100 IU is sort of a magical number because it's the number that has been shown in supplementation studies to significantly decrease the occurrence of cancers and coronary heart disease.

I have a couple of predictions for the coming decade. We'll be able to manipulate to some degree most of the vitamin pathways in plants, as well as some of the biosynthetic pathways affecting the uptake of minerals such as iron and zinc. The genes for other nonessential compounds will also be isolated, and we'll be able to manipulate them too. The real question is whether we'll be able to use this knowledge to address some problems in the real world, not only in the developing countries but also in the developed countries. There has already been manipulation of beta-carotene in rice, yielding a product called "golden rice" with enhanced vitamin A synthesis. It is being targeted to the developing world in an attempt to alleviate vitamin A deficiency, which results in blindness in 250,000 children a year.

Questions and Answers

Question: To make these genetically engineered plants, you need a selective mechanism in order to find the plant that has the gene you want, and often that selectable marker is antibiotic resistance. Does the gene coding for that antibiotic resistance hang around in the final plant, in the final piece of food, and does it pose a risk?

Roger N. Beachy: Your question has been addressed in the past 10 or 12 years. There are two issues: first, will the DNA in the plant that encodes this antibiotic resistance be taken up by the *Escherichia coli* in your gut and then allow the *E. coli* to be resistant to the same antibiotic? The chances are extremely low because the DNA that is used is made for eukaryotes, relatively advanced organisms with an organized nucleus. It doesn't work for prokaryotes, which are more primitive bacteria; they have different regulatory sequences in front of them and are not likely to be active. Second, the chance of the DNA from the plant actually being incorporated in the *E. coli* is also extremely low: it has not been found to date. Also, the antibiotic selected for this experiment back in the mid-1980s was an antibiotic called kanamycin, a very old antibiotic that is rarely used any more in human health. It's not normally used in therapies for infections. However, the perception by the public of a potential risk, not an actual risk, was such that companies are actually engineering out the utility of this antibiotic resistance marker—not because it's a danger, but because the public is concerned.

Daphne Preuss: I want to add that the measured frequency of this potential transfer is far lower than the frequency of spontaneous kanamycin resistance in the bacteria already. So even if this transfer can happen, the frequency at which it happens is much lower than that of other events that go on all the time.

Question: What are the best practices for universities to adopt to ensure effective transfer of breakthrough technologies to the private sector for public benefit?

Roger N. Beachy: Universities are charged with discovery; companies and corporations are charged with development of discovery to actual utility. Sometimes the scientists themselves do that development; in other cases they license it out. In the past 10 or 15 years, with the advent of biotechnology, universities have looked at licenses from biotechnology as a potential golden goose and have indicated that they expect that financial development can accrue, as was the case with engineering, software and hardware in the computer industry, and other examples. As a result, when companies come to negotiate for contracts, they often ask for exclusive rights. Universities have largely given in to the pressure that has come from the private sector. The trouble with this arrangement is that they don't reserve the right to use the discovery for other purposes, such as humanitarian efforts. My own experience is that once you assign intellectual property to a corporation, the chance of getting it back for humanitarian purposes is very low. It's very difficult. Lawyers always cover their backsides, and companies have their own policies, and universities have given in to the pressure of the private sector and signed away more than they need to. At the Danforth Center, we retain the right to use our discoveries for humanitarian purposes. We don't sign exclusive deals; we sign deals that allow use in the United States and the developed countries only. Interestingly, five companies have agreed to our terms so far. It took 15 to 20 years for the pharmaceutical industry to begin addressing needs in developing countries. Food companies, on the other hand, have already turned the corner and are allowing their technology to be used for developing countries.

Dean DellaPenna: The engineering of beta-carotene synthesis into rice, primarily for Southeast Asia and parts of India, where 250 million people a year are deficient in vitamin A and 250,000 children go blind and die every year, required the waiving of close to 70 patents that were held by various companies and universities. Much to my surprise and pleasure, all the parties stepped forward and waived the rights to enable Africa and Southeast Asia to benefit from this "golden rice" invention.

Robert Haselkorn: The golden rice story is not finished, I'm sorry to say. Feeding experiments suggest that people now eating this rice as the main food in their diet may still not have enough vitamin A because there's a problem absorbing vitamin A in the gut if you don't have enough ancillary fat in your diet. So, although golden rice is wonderful, a lot more has to be done.

Roger N. Beachy: There's another part of the story, however, that gives us hope. Another technology has put vitamin A into mustard seed oil, so it is in a lipid form.

Daphne Preuss: One of the frustrations, though, is that everyone is looking at each product so critically. If it turns out that the golden rice is not as great as first expected, there will be a big backlash. Each discovery almost has to be a home run because of the political pressure on the field right now. Any industry or technology needs a little time to optimize.

Question: A lot of the resistance to the genetic modification of plants has come from Europe and other countries, yet a lot of your targets are the undeveloped countries. Is there resistance in the undeveloped countries, along the lines of "What are you trying to dump on us?" and "This is bad stuff"?

Daphne Preuss: Some countries embrace agricultural biotechnology wholeheartedly; Argentina and China do, for example. Some countries, such as India and Brazil, are very nervous about it. And some countries are very angry about the arrogance of Europe and the United States in telling them not to use technology.

Robert Haselkorn: There is a great story about genetically engineered soybeans. The European Union prohibited the importing of genetically engineered soybeans because it was opposed by the Greens on environmental grounds. The Greens' position happened to coincide with the economic interest of the European soybean producers: if you prohibit genetically engineered soybeans, you exclude American soybeans. All of a sudden, the countries of the European Union required US soybean meal to feed their animals, because the BSE (bovine spongiform encephalitis) epidemic in Western Europe necessitated the elimination of animal waste as a source of feed for livestock. Genetically engineered soybean meal is just fine with the European Union now. It was an economic issue in the guise of an environmental issue.
