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Molecular Farming

Using Biotechnology in Agriculture for the Sustainable Production of New Materials

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This publication is part of a series that seeks to provide science-based information about discoveries in agricultural biotechnology. The information in these publications comes from the Biotechnology Research and Education Initiative (BREI) committee, which comprises a multi-disciplinary team of research, extension, and teaching professionals from the College of Agriculture. The series is designed to help Kentuckians understand and assess the risks and benefits of agricultural biotechnology.

BREI

Introduction

The science of biotechnology, now some 20 years old, has long promised the prospect of adapting agricultural crops and livestock to entirely new purposes. Just as genetically engineered bacteria have become routinely used for economical, efficient production of a wide range of medicinal proteins and industrial enzymes, plants and animals may be engineered to produce a variety of valuable biological molecules ranging from medicinals such as vaccines to polymers such as biodegradable plastics.

Molecular farming: Using genetically engineered plants and animals as production systems for modified and novel materials.

The advantages of molecular farming are obvious: biologically derived substances are most efficiently produced through biological means, utilizing natural and renewable resources and ensuring optimal environmental compatibility. The outcome will be the creation of new markets for farmers which complement their existing business.

The "proof of concept" has been available for many years in the form of numerous examples of transgenic (genetically engineered) plants containing a variety of new products in their leaves or seeds and transgenic animals producing therapeutic proteins in their milk. Some changes in production methods may be called for, as with the adoption of any new plant or animal as an agricultural commodity; for example, tobacco producing new materials in the leaf might be machine-harvested green prior to extraction and purification of the product. Nevertheless, it is anticipated that molecular farming will relate directly to traditional agricultural skills and resources.

The onset of the 21st century brings the welcome prospect of transition from "experimental" status to profitable opportunities for farmers. This publication summarizes the current status of commercialization efforts and illustrates some of the exciting new opportunities that are at an advanced stage of development.

How Does Molecular Farming Work?

Until recently, improvement in an agricultural enterprise relied largely on breeding programs to increase the productive capacity of crops and livestock. But now genetic engineering makes it possible to introduce entirely new characteristics very efficiently, by inserting the gene(s) coding for the desired characteristic directly into the genetic makeup of a plant or animal. This technology utilizes nature's own resources and is both specific and precise—only a defined minimal set of genes is introduced into the host. Genetic engineering is thus substantially more efficient than traditional breeding. Additionally, the ability to insert nonnative genes allows plants and animals to produce entirely new materials for innovative applications.

Plants, in particular, have long been used as a source of natural chemicals and materials, such as flavorings, fragrances, medicines, dyes, rubber, and oils. By adding or deleting genes from these plants, it is possible to change the characteristics of the products or create entirely new ones. For example, rapeseed (canola) oil, which is normally used for cooking and margarine production, has been modified not only to be healthier for cooking, but also for use in manufacturing detergents and novel lubricants. Soybeans have also been engineered for novel bio-based lubricants that are renewable and fully biodegradable and that have fewer risks for humans and the environment in shipping, handling, and production. In certain

Molecular farming may include machine-harvesting green tobacco for the new materials produced in its leaves.

applications, these lubricants may be competitive with petrochemical-derived lubricants. In another example, tobacco has been engineered to manufacture numerous products including antibiotics, novel polymers, a dental treatment, and anti-cancer drugs. Dozens of compounds have been produced in a whole host of crop plants ranging from traditional commodity crops like corn, soybeans, and tobacco to specialty crops like spinach, potatoes, and beets.

Several pharmaceuticals made in this way in plants are in late-stage clinical trials and are expected to reach the market in the very near future. The potential of plant molecular farming for these types of pharmaceutical and industrial proteins is considered huge because of the ease of scaling up their production from experimental levels to field production (this is commonly called scale-up) and their predicted low production costs. Some highly valuable pharmaceuticals that are needed only in small quantities will likely be produced on a very small scale (e.g., in a greenhouse). Other products such as biodegradable plastics, which are presently at an earlier stage of development, may eventually require thousands or even millions of acres for production.

As **molecular farmin**g production becomes more efficient, larger-scale, lower-value products such as industrial chemicals or biodegradable plastics should lead to larger-scale opportunities for agricultural producers.

There is also considerable interest in livestock-based production systems. Goats, pigs, cows, sheep, and chickens have all been engineered to produce a variety of new proteins, mostly for the medical industry. Advantages touted for these systems are their relatively low operating costs and unlimited scale-up. Another benefit of the animal-based systems is that the desired protein can be produced in the milk of mammals or the eggs of hens, potentially allowing easier extraction and purification. As an example, one recent announcement in animal molecular farming is the scale-up of a herd of goats engineered to produce a spider's web protein in their milk. It is suggested that this "biosteel" will revolutionize the materials industry, as it is both stronger and more flexible than steel and offers a lightweight alternative to carbon fiber. Potential uses include applications for which strength and lightness are essential, such as aircraft, racing vehicles, and bulletproof clothing, and for artificial tendons, ligaments, and limbs. In addition, 40 to 50 pharmaceuticals are already under development for production in animal systems; at least two reached late-stage clinical trials in the summer of 2000.

Economics and Commercial Opportunities

It is difficult to generalize about the economic viability of molecular farming systems. Each application is different, with variation in farming practices, efficiency of the gene-expression system, ease with which the product can be extracted and purified, and prospects for obtaining useful by-products (e.g., seed oil and meal). One would expect plant systems to be different from animal systems, but there are extreme contrasts even among the plants and animals. For example, tobacco is a very different crop compared to corn, soybeans, or canola. Tobacco has the advantage of producing large quantities of green leaf material per acre, and it is very convenient to work with from a biotechnology standpoint. Because of these qualities, tobacco may be the ideal "factory" for products produced in green leaves. In cases where the products need to be produced in seeds, a better choice may be corn, soybeans, or canola because tobacco seeds are extremely small. All crops have different genetic composition, different characteristics, and different production methods, making each a unique "vehicle" for molecular farming.

Because of these differences, there is no way to establish the "cost" of generating a product using molecular farming. Some estimates are based on predictions of crop or animal production costs, necessary capital investments for processing facilities, etc., but these range from dollars per gram of product produced to thousands of dollars per gram. However, certain principles are quite clear: for both plants and animals, profitability requires high expression of the introduced gene, maintenance of product integrity, and the ability to scale up, harvest, recover, purify, and store the target product as cheaply as possible. For products that require high purity, the processing and purification costs are expected to be very high.

The commercial scale-up of molecular farming is now beginning to happen. Many suitable products have been identified, especially in the medical field, and the technology is being perfected for large-scale implementation. High-value pharmaceuticals are expected to be the first products of molecular farming owing to their high profit potential, and many such products are under development and in clinical trials from both large and small companies. For success in the competitive marketplace, scale-up cost cutting will be critical, particularly in the area of purification and product recovery. Ultimately, if the products and processes of molecular farming are to be commercially successful, they must hold a competitive advantage over existing, alternative products and processes (e.g., pharmaceuticals produced through microbial fermentation). Or, if the products are entirely new (e.g., biodegradable plastics or "biosteel"), there must be a corresponding new market for them. As this technology continues to develop and molecular farming production becomes more efficient, then larger-scale, lower-value products such as industrial chemicals or biodegradable plastics should lead to larger-scale opportunities for agricultural producers.

The environmental and process regulations are just now being developed for this industry. It will be necessary to establish a regulatory regime that strikes an acceptable balance between safeguarding the public and the environment and sustaining the innovative process. In the area of environmental release, the critical scientific questions are now being addressed.

While the commercial progress is very exciting, molecular farming is still very much an emerging industry. The farm-level opportunities will undoubtedly start small, but they will grow over time. Contract production is likely, and profit margins may vary considerably depending on the value of the target and the increased production requirements. But the unique thing about molecular farming is that this opportunity should provide a captive new market for agricultural products, one that can increase over time and one that should provide the pioneer producers with a clear advantage.

Molecular farming with crop plants, and in particular with tobacco, is well suited for Kentucky and can now be added to the list of emerging enterprises in the commonwealth.

Molecular Farming in Kentucky

Kentucky's farm economy historically has depended on the production of tobacco. However, the long-term economic potential for tobacco remains uncertain at best, and thus there is considerable interest in developing molecular farming as a new opportunity. Kentucky agriculture is changing, with new niche markets, value-added activities, and new enterprises entering the diversification mix. Agricultural producers in the state can now decide on a whole host of enterprises ranging from traditional commodity crops to new nontraditional activities such as meat goats, freshwater shrimp, and blueberry production. No crop mimics the small acreage requirements and the large potential profits of tobacco for many producers. But molecular farming with crop plants, and in particular with tobacco, is well suited for Kentucky and can now be added to the list of emerging enterprises in the commonwealth.

Already one molecular farming company is located here. Large Scale Biology recently built the world's first bioprocessing facility in Owensboro to process tobacco for the production of biopharmaceuticals. Elsewhere, companies such as Prodigene in College Station, Texas, and Integrated Protein Technologies in St. Louis, Missouri, are using corn or soybeans as their production system.

To assist the development of tobacco molecular farming for Kentucky, the Tobacco and Health Research Institute (THRI) at the University of Kentucky has undertaken a major refocus of its mission. Collaborating closely with the UK College of Agriculture, THRI has established a comprehensive tobacco biotechnology program to assist in the development of new crops based on transgenic tobacco. This new program explores the use and potential of genetic engineering to create molecular farming opportunities for Kentucky tobacco farmers. In addition to scientific research, THRI is also seeking industrial collaborators to identify products that could generate expanding new markets with the hope of attracting new commercial interests to the commonwealth.

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