Chemistry & Biology, Vol. 10, 893–894, October, 2003, DOI 10.1016/j.chembiol.2003.10.006

Innovations

Metabolix, Inc. and Tepha, Inc.

Bioplastics for Industry and Medical Devices

Traditionally, the plastics and specialty chemicals industries have been led by familiar names like Dow, Monsanto, and DuPont. But since 1992, a small company has been making inroads into commercial production of environmentally friendly specialty polymers and chemicals—a market growing in consumer demand and product options. Metabolix, a 30-person operation headquartered in Cambridge, MA, is in the business of making a versatile family of biologically derived polyesters called polyhydroxyalkanoates or PHAs. At the heart of the company's current production capabilities are genetically modified bacteria able to synthesize large amounts of PHA plastics from renewable, nonpetrochemical sources.

Fermented at MIT

Metabolix owes its conception to founders Oliver Peoples, PhD, Anthony Sinskey, ScD, and Simon William, PhD, three MIT researchers working in the fields of molecular biology and biochemistry. Beginning in the mid 1980s, the trio recognized the potential for metabolic gene technology strategies. "There was quite a bit of activity implementing gene technology strategies with the goal of improving bacterial strains to produce therapeutic proteins," recalls Peoples, now Chief Scientific Officer at Metabolix, "but we were interested in biopolymers in particular."

The researchers then set to work using genetic engineering to control the pathways or chemical steps leading toward improving biologically based PHA production in bacteria. "If we could dictate what pathways were followed, what molecules were made, and what molecules were polymerized, we theorized we could then make any kind of polymer we wanted," says Peoples. "The basic idea was to use genetic engineering to produce polymers more reproducibly, cost effectively, and with a broader range of performance than could be done with natural strains."

MIT filed the first patents on the concept that genetic engineering would play a crucial role in developing manufacturing technology for PHAs. MIT identified and patented the key genes and the use of the genes to make these PHA materials. Metabolix licensed the patents in 1993. "Since that time, we took the basic MIT genes and developed a broadly enabling platform technology to build our robust production strains," says Peoples.

Lots of soil bacteria produce PHAs, which are essentially a reserved energy deposit within the bacteria. "Instead of making starch, carbohydrate, oil, or fat, as most organisms do, at some point these bacteria evolved to make PHA polyesters as their retained energy source," says Peoples. He and his colleagues discovered a way to genetically alter the bacteria to produce much larger quantities of the polymer. Metabolix's bacteria today are essentially morbidly obese cells composed of nearly 85% PHA biomass derived via fermentation of natural sugar and oils.

> "Instead of making starch, carbohydrate, oil, or fat, as most organisms do, at some point these bacteria evolved to make PHA polyesters as their retained energy source." –Oliver Peoples, PhD, Cofounder and Chief Scientific Officer, Metabolix

Commercializing PHAs

Metabolix's strength is in engineering bacterial strains to make PHAs through fermentation. Other companies will then apply those materials for their own applications. "Our purpose now is to commercialize PHAs with strategic alliances with other companies and see that they enter the marketplace," says CEO Jim Barber, PhD, an organic chemist who has spent his career in the specialty chemicals and materials industries.

"We're a 30-person company in a vast 300 billion pound plastics industry," says Barber. The company's plan is to achieve a market presence through partnerships such as the applications evaluation collaboration with BASF announced in July 2003.

"We are now at the threshold where PHAs are about to enter the marketplace, as they are now in prototype in a number of different application areas," says Barber. A key milestone in the commercial success of PHA products has been Metabolix's demonstration of PHA manufacturing at 60,000 liter, industrial-scale fermentation.

Metabolix is not alone in its quest to provide more environmentally friendly plastics. DuPont has been developing polymers from corn-derived 1,3-propanediol, or PDO, with hopes of a 2004 commercial launch. Cargill Dow is working on NatureWorks PLA, a biopolymer derived from lactic acid. Others in the arena include Maxygen (through its Codexis subsidiary), BASF, Procter & Gamble, Hercules, and many academic and research centers worldwide. Metabolix is able to compete because of its strong intellectual property position surrounding its genetic engineering technology. "Our IP position prevents others from using genetic engineering to boost production and control composition and properties," says Peoples.

Applications

Biology makes essentially 4–5 polymer types including proteins, polysaccharides, and nucleic acids. Almost all of them interact with water, making them poor candidates for barrier materials. PHAs are unique in that they are true high molecular weight polyesters and are very diverse. Nearly 100 different PHA building blocks can be engineered, but only about 10–12 are relevant for making functional polyesters. "The different building blocks are made in the fermentation process with the bacterial strains," says Barber. "The key here is that we are putting the pathways into the cell of the bacteria to convert sugar and other raw materials into the building blocks we want. Then, that same cell polymerizes them into high molecular weight polymers very efficiently." By changing the pathways, the type of building block created and then assembled is altered.

"With several of these building blocks, we can achieve a wide range of material properties, from hard and rigid to elastomeric and highly flexible," says Peoples. They achieve these different properties by combining different ratios of those building blocks. The company is currently focused on three prime application areas. These include injection-molded biodegradable materials, for which the company received a grant from the Department of Defense, paper coatings that allow paper to be recycled or degraded, and flushable fibers for nonwoven materials such as those in personal hygiene products and wipes. Other areas of interest include adhesive applications and renewable packaging products.

Growing Plastics

In 2001, Metabolix received a $7.4 million grant from the Department of Energy for development of PHA production directly in plants. This follows the creation of a modest program to produce PHA in plants that began in 1998. "The plant program is a significant portion of our R & D effort and is going to be the ultimate answer to sustainable manufacture of polymers," according to Peoples. "And we know we will be able to produce these PHAs in plants, recover the polymers, and use the plant residue for electric power generation." The hoped-for net impact will be that the polymer production will produce excess energy and fix significant amounts of environmental CO_2.

"The fermentation system is extremely flexible, so you can make a wide range of different materials with a high degree of control," says Peoples. "And it has brought us to a cost structure nearing $0.50/lb that is very attractive for some mid-level plastics markets," adds Barber. But they both concede that plant science will be limited in the flexibility of its output. Only a small number of PHA commodity-type plastics will be made directly in plants. "But the cost will probably be less than petrochemical polymers, and we cannot get that with fermentation," says Peoples. "We know that to carry the day we cannot just rely on biodegradability and sustainability," says Barber. "It's a great tie breaker, but we know our products have to be economically competitive to enjoy widespread use." Realizing this, Metabolix aims to produce the PHAs in plants at a cost below $0.30/lb. "That means we will be economically competitive with polyethylene and polypropylene," says Barber. "In other words, if we get this technology up to scale we will have a disruptive technology that will affect the whole thermoplastics industry."

Plants do not naturally make PHAs, but Metabolix has proven plants can grow them by genetically engineering the same basic genes described in the initial MIT patents. The company is using native switchgrass plants, a perennial nonfood crop requiring little fertilizer or pesticide. "Our challenge now is to work on optimizing that system to make significant levels of polymer and also healthy plants," says Peoples. Commercial applications are years away, although the effort got a boost in September 2003 with an additional award from the USDA.

Medical Devices

In the late 1990s, Metabolix cofounder Simon Williams began to foresee medical applications for the company's polymer technology. He and others involved with Metabolix quickly realized that the issues involved in a highly regulated niche market such as medical devices differ largely from those focused on large commercial-scale applications, where cost and scale are significant concerns. Thus, in 1998 Tepha, Inc. was incorporated and spun off from Metabolix with Williams as President and CEO. The 6-person company is located blocks from its sister company in Cambridge.

"We plan on making a variety of medical products ranging from relatively simple medical devices, such as sutures and meshes, to orthopedic devices to bioengineered heart valves," according to Ajay Ahuja, MD, Tepha's Director of Business Development. They are primarily using two strong and flexible PHA biomaterials, TephaFLEX and TephELAST, with TephELAST being the more flexible and elastic of the two. "Given the physical properties of these PHAs—strong, flexible, extensible—the fact they are absorbable and tissue friendly, and that we expect to be able to control the rate of absorption, we hope to fit any medical need we investigate," adds Ahuja.

With its TephaFLEX product, Tepha is also working on more flexible polymer-based coronary stents. They are also working on a drug delivery technology loading drug into polymer-based stents similar to the drug-eluting stents introduced commercially this year. Regenerative medicine in the form of tissue engineering is a key long-term potential opportunity for the company. Specific applications include a replacement heart valve and a cell-seeded vascular patch, both developed in collaboration with Children's Hospital in Boston using TephaFLEX. In 2002, Tepha received a $3 million grant from the National Institute of Standards and Technology's Advanced Technology Program for its tissue engineering biopolymer scaffold program.

***Chemistry & Biology* invites your comments on this topic. Please write to the editors at chembiol@cell.com.**

Alice McCarthy is a freelance science writer based in Gloucester, MA (alice@alicemccarthy.com).