Researcher engineers microbes to produce compounds that can be used in industrial processes

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MIT Department of Chemical Engineering Associate Professor Kristala Jones Prather Credit: David Sella

There's an advantage to working with natural materials: They already

exist. Their locations are often known and their behaviors are somewhat predictable. But those are also disadvantages, as resources can become scarce and applications static.

Kristala Jones Prather, the Theodore T. Miller Associate Professor of Chemical Engineering at MIT, looks to change that in her lab by engineering microbes to make new compounds. While challenges lie in increasing scale and maximizing yield, all in the need to be competitive, there's also potential. With her private sector experience, Prather understands the requirements of research and the realities of commerce. Getting them to co-exist could help lead to chemicals that lower drug costs and replace petroleum through alternatives that are easy to adopt, and, most importantly according to Prather, profitable.

Different questions, different answers

A standard initial question in product development is: "What does this existing material do?" It's logical and provides a roadmap, but it's also limiting. Prather takes a different approach. She looks at a material's chemical constituents for their end utility. Her starting question now becomes, "What properties are needed and how can they be encoded?"

One compound she's working on is 3-hydroxy-gamma-butyrolactone, a building block for pharmaceuticals. The material is currently available through chemical processing of petroleum-derived precursors, but the synthesis is expensive. The hope, Prather says, is that the biological processing that she's developing in her lab would lead to less expensive drugs, particularly statins and a new category of antibiotics.

A second compound is glucaric acid. It's demonstrated potential as a de-icer in road salts with lower environmental impact, and to be converted to adipic acid, a central ingredient in nylon 66, one of the largest volume materials on the market. The acid may also be useful to produce super-

adsorbent polymers—in diapers, for example—and other multi-functional materials, allowing them to be incorporated into new resins and coatings.

Essentially, the fundamental bioconversion technology in which sugars, mostly glucose, are used to access needed structures could reach into anything that currently involves petroleum, be it bio-fuel, clothing material, or plastic computer casings. "This is a way for us to think about expanding the so called bio-economy," Prather says.

Curbing a cell's appetite

Economic obstacles help guide Prather's work. She picked glucaric acid and 3-hydroxy-gamma-butyrolactone, she explains, because production costs on both are high and restricts market uptake. While each might be environmentally friendlier than and reduce dependence on petroleum-based alternatives, being green isn't enough. A compound or process has to be profitable and as effective as industry standard, ideally more so. "We have to compete with what existing market there is," she says.

One challenge with developing these processes is that cells by nature want to eat sugar in order to grow and divide; they have no motivation to do otherwise. Prather and her team have developed biological "devices" that would manipulate the cells to eat, stop, then convert the sugar to a desired product. To do that, they identified an essential protein associated with sugar consumption in a cell, then engineered the cell so an added chemical inducer can control whether that protein is "on" or "off." With the protein turned down, the cell can't eat the sugar for growth, and, without the competition, the desired product can dominate the process and higher production levels are reached, she says.

Achieving that regulation has helped improve yield. For her technology to be attractive, as much possible initial material needs to be in the final

product. To that end, her lab has increased the yield of a model compound from less than 1 percent to over 35 percent in one organism and over 80 percent in another, she says.

Prather's main objective with her compounds is that the transition to market be seamless. When it comes to fuel, for example, car engines are well established. There doesn't need to, and can't, be different engines or major infrastructure changes. Any extra hurdle would stifle the consideration, let alone the adoption, of a new product, she says. But, in other areas, there's the chance to make things better.

Prather is looking to integrate processes that would make it easier to take a strain created in a lab and produce it in a large-scale facility. As it stands, most chemical production uses a continuous process; a plant will often run for 50 weeks out of the year before it's stopped for maintenance and then re-started. Most biological manufacturing uses a batch process in which the facility runs several days to a couple of weeks.

A continuous process is frequently more efficient and productive, but contamination is a holdup issue, she says. If a foreign microbe enters into a facility, it would have to be shut down until the situation is fixed. Prather is looking to develop technologies that would make naturally sterile environments for specific microbes. One option is to use organisms that are resistant to the toxic effects of a particular growth environment. In this way, any contaminant would not be able to survive the hostile environment, while the production organism would continue to grow and make product. The hurdle is a lack of good tools to engineer these novel microbes, a challenge that Prather says her team is currently tackling.

The happy co-existence

The need to have compounds that are not just effective but also viable comes from experience. Before academia, Prather worked in the pharmaceutical industry for four years and first came to understand how to bridge the economic needs of a process and the functional needs of a product. The balancing act has been furthered since she's been on campus and worked with various pharmaceutical and oil companies, she says.

A key element is that the partnership starts with each side being up front with its needs and objectives and continues with constant feedback. "That's when it works best," Prather says. The result is that industry gets a sense of what it takes for a technology to leave the lab, and academics, particularly students, are able to see what happens once that technology enters the commercial world.

Overall, she says, a partnership doesn't have to be two separate spheres merely co-existing for a finite amount of time, since common desires and purposes exist. While academics are focused on research and understanding principles, and can't deviate from that, Prather says, "We're also very much excited about the potential of having those findings and that research translated into something that shows up in the marketplace."

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