RICE THAT COULD SAVE LIVES

AND OTHER DISCOVERIES YOU'VE NEVER HEARD OF

By Nate Seltenrich

Accounting for more than 1.5 million deaths a year and 17 percent of all childhood mortality, the No. 2 killer of children worldwide is not measles, malaria, AIDS, or any other malady we fear as if by reflex. Instead, it's something we've learned to live with in the United States, where it rarely turns deadly. In the developing world, diarrheal disease is second only to pneumonia in causing deaths among children under five, killing more children every day than malaria, AIDS, and tuberculosis combined.

Peggy Lemaux and **Bob Buchanan** think their technology could help—if only the FDA approved. Using genetic engineering techniques developed through their work in the Department of Plant and Microbial Biology (PMB), the pair devised a method to overexpress individual proteins within the grains of cereal crops such as wheat, barley, and sorghum. When California biotech company Ventria Bioscience caught wind of their innovation in the late 1990s, it immediately saw the potential.

Using Lemaux and Buchanan's platform, Ventria found a way to use rice crops to produce two proteins, lactoferrin and lysozyme, which occur naturally in breast milk and have been shown to provide a range of health benefits for young children. The genetically engineered rice plants (also known as genetically modified organisms, or GMOs) produce a rice grain containing large amounts of the proteins, which are then extracted, purified, and used to formulate a preparation that improves the sort of anti-diarrheal rehydration solutions already consumed by half the world's children.

In a 2007 study involving 140 children in a Peruvian hospital, researchers from Ventria and the University of California, Davis, found that the treatment not only reduced the duration of diarrhea in afflicted children by nearly 30 percent, but also lessened the diarrhea's severity and the number of recurring episodes. In a related study at Johns Hopkins, the preparation dramatically enhanced recovery from diarrhea in adults, a common ailment among hospital patients taking antibiotics. Although not tested, these results seem to indicate that the rice product could alleviate some of the effects of cholera—a worldwide scourge that in recent months has taken thousands of lives in Haiti.

In 2004 Ventria's product received the "Generally Recognized as Safe" label from an international panel of academic experts who specialized in pediatrics, immunology, and allergies. The product was quickly submitted to the FDA for approval as a food supplement, which would enable it to be brought to market. The company expected to receive approval in six months to a year. Instead, all it heard was silence. Concerned that their documentation may have been too broad, Ventria scientists modified the notification to target pediatrics, and resubmitted it in 2007. But three more years passed without a response, and in March of 2010, Ventria withdrew its notification a second time, not knowing where to turn next. "We're sort of stuck in limbo right now," said Scott Deeter, the company's president and CEO. "The potential and the benefits are so enormous. It's hard to give up on it."

Meanwhile, Lemaux and Buchanan feel that a golden opportunity to potentially help save countless lives is being missed. The FDA has not told Ventria why it refused to review its oral rehydration solution, but the Berkeley researchers believe they know why: there is a hesitancy to approve products from genetically modified organisms. "It's simply the GMO issue," said Lemaux, a PMB Cooperative Extension Specialist, who has researched genetic engineering at UC Berkeley since 1991. "That's what the concern is here. They have to be much more cautious than they do with other food supplements."

As Lemaux sees it, the root cause is that the FDA isn't sure how to move forward in this situation. Certain food-safety and environmental groups have launched high-profile campaigns against GMOs, emphasizing potential biological and environmental impacts. As a result, Lemaux argues, regulatory agencies are likely wary of approving such products.

"If you could do this without genetic engineering, there wouldn't be nearly as many concerns," she said. "People want to talk about risks. But there are risks on both sides. In this situation there are risks if you don't do it. The suffering of a lot of people might be spared."

Controversy and innovative science have gone hand-in-hand since the days of the sun circling a flat Earth. More recently, embryonic stem-cell research has kindled ethical quarrels yet to be resolved. Looking forward, robotics and nanotechnology could well be the stem cells and genetic engineering of the future. All hold the potential to both solve and cause problems, and our society appears divided on whether or not to embrace them. As these tensions play out, significant breakthroughs are sometimes lost in the shuffle.

Disagreements over controversial science often boil down to differing perspectives on calculations of risks and rewards. Proponents stress a particular reward, or the cost of inaction. Opponents may concentrate on related risks, or employ the precautionary principle to place burdens of proof on those taking action. One can almost see the scales swaying.

The GMO issue is much broader than biopharming, the term used to describe the production of pharmaceutical agents through crops, such as in Ventria's work with rice plants. Within the United States, hotly contested debates surrounding genetically engineered salmon, alfalfa, corn, and other organisms have also brought an ideological divide to light. The same divisions are evident at the university level, and even within the College of Natural Resources. Environmental Science, Policy, and Management Professor **Miguel Altieri** is a staunch opponent of the genetic engineering of crops, having written numerous papers criticizing biotechnology. As an alternative to genetically engineered crops, he focuses on developing methods that employ biodiversity and traditional farming practice to sustainably boost food production.

Professor Emeritus **Andrew Gutierrez**, also of the Department of Environmental Science, Policy, and Management, is another skeptic. He says the scientific testing that goes into many GMOs prior to production is of dubious quality, making it difficult to foresee environmental risks related to cross-contamination and effects on other species. "It's not a system I would trust," he said.

The result is a scenario in which scientists often find themselves pitted on one side or the other of the GMO debate. "There's very little meeting of the minds, which is unfortunate," said Lemaux. But in the end, she adds, this may be no cause for despair: "That's the nice thing about being at a university—you can pursue your own ideas, even if they don't match with what other people are doing."

Buchanan, PMB professor and CNR's Executive Associate Dean of Research and Extension, who has been at UC Berkeley since the early 1960s, puts the disagreement more succinctly: "It's just different philosophies."

While both Lemaux and Buchanan say they're disappointed that the diarrheal treatment has yet to see the light of day, it's not their only source of frustration. Some of their other discoveries have stalled at even earlier stages. In 1997 they used their protein-expression technique to begin creation of a wheat variety that was less allergenic, but they failed to find a partner to further develop it. However, this research led not only to the pair's interactions with Ventria, but also to a further innovation they believe could have a huge impact on worldwide food production. A group of Chinese researchers learned about the pair's work and figured out a way to apply some of the same genetic solutions to a significant problem facing farmers in China and around the world: pre-harvest sprouting in white wheat.

The problem occurs when seeds sprout before the plant is ready for harvest, often triggered by rain and high humidity. As much as 20 percent of China's wheat is lost to pre-harvest sprouting each year. Yet a field test of genetically modified white wheat that resists pre-harvest sprouting was planted in 2007 by researchers from Henan Agricultural University and they are currently growing the fourth generation with no reduced yield, Buchanan said.

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Now the Berkeley researchers hope to apply the same approach to wheat that is of value to the United States, where pre-harvest sprouting in white wheat results in millions of dollars of losses every year. Not only would the change result in significant savings, but it would also allow many growers to switch from red wheat to white wheat, which has more nutrients and fiber. A Montana-based wheat-breeding company initially expressed interest, Lemaux said, but it was recently bought by a larger corporation that has not expressed interest in pursuing the approach.

Lemaux isn't giving up. She's actively seeking grants and partnerships that may help support implementation of modified white wheat in the U.S. Upcoming meetings on pre-harvest sprouting in Brazil and Canada, where she will present this work, may help attract some interest—and, ultimately, funding. Still, all the obstacles have taken a toll. "I pick my projects carefully, ones that I think would have some positive impact on agriculture if they were able to get out. The fact that none of them has made it is quite frustrating," she said.

"I wish we could take the wheat work further, because I think there's a lot of promise there," echoed Buchanan. "It could change the way wheat's grown, and the kind of wheat we grow."

Lemaux chalks up some of the challenges with modified wheat in the United States to nervousness about genetically engineering what's known as the "staff of life." But many critics and fellow researchers have expressed practical concerns, perhaps the largest of which is the cross-pollination that can occur when genes from genetically engineered crops mingle with those of non-engineered crops or organic crops.

Santa Clara University professor **Michelle Marvier**, who specializes in risk assessment of genetically modified plants, views gene flow—known as out-crossing—as an inescapable byproduct of genetic engineering. "It's going to happen," she said. "They have no success to date at keeping any genetically modified crop contained. There's a huge list of examples of genetically modified genes getting out of the lab before they're even released."

While Marvier doesn't view out-crossing as an inherently bad thing, she says it can be highly problematic for some modifications. With herbicide tolerance, genes in food crops or grasses could spread to nearby plants and create so-called superweeds that are resistant to certain herbicides. She's also wary of biopharming. While lactoferrin and lysozyme occur naturally in breast milk and are relatively benign, other proteins such as human growth hormone could pose serious problems if they were to make their way into the food system via GMOs, Marvier said.

Both rice and wheat are almost exclusively self-pollinating, dramatically reducing the chances of cross-pollination, Lemaux said. On top of that, most genetically engineered crops are planted a significant distance from non-engineered crops in order to further reduce the odds of gene movement. Lemaux agrees with Marvier that the risk of commingling is never nil; something as simple as a seed spilling off a truck could cause a variety to end up somewhere it's not supposed to be. The debate returns again to the question of risk versus reward: what might happen if we act, and what will happen if we don't?

Tempting as it may be to dwell in the past, Lemaux and Buchanan keep their gazes fixed straight ahead. In recent years they used similar technology in a partnership that sought to increase the nutritional content of sorghum, an important food crop in Africa. The research received funding through both the United States Agency for International Development and the Bill and Melinda Gates Foundation's Grand Challenges for Global Health. They've since passed their advances along to another partner in the project, the Council for Scientific and Industrial Research, a Johannesburg-based organization, and hope someday to see them implemented. Even in the absence of further funding, Lemaux and Buchanan continue to work on improving the nutritional qualities of sorghum, largely with undergraduate students in their Koshland Hall laboratories.

Motivated by a desire to make a lasting contribution to agriculture, Lemaux and Buchanan—who both grew up on farms; he in Virginia, she in Ohio—maintain hope that someday beneficial GMOs will be widely accepted within the United States and around the world. Buchanan likens the gradual eroding of public opposition to waves wearing away at a rock: "It'll happen," he said. "Slowly, I guess, but it's evolving in that direction. It'll happen."

He may be right, but in Marvier's view, opinions deserve to be more nuanced. "There's a million things you can do with the technology, and some of them are going to be really good, some of them are going to be frivolous, and some are going to be harmful," she said. "It's just case by case. You can't lump them all together and say 'I'm for it or against it.'" Lemaux and Buchanan agree. The answers, it seems, are never easy. 31