



# Unlocking the Key to Autoimmune Disease

*Discoveries in the lab lead to  
promising treatment trials  
for celiac sufferers*

BY SUSIE FLAHERTY

**Ser-en-dip-ity (ser'en dip' e te) n. 1. A seeming gift for finding something good accidentally.**

The word serendipity is one of those oddities of the English language. It is not derived from Latin, Greek, Hebrew, Old English or any written language. It was coined in 1754 after the publication of *The Three Princes of Serendip*, a Persian fairy tale filled with the lucky discoveries of the three princes of Sri Lanka.

But serendipity is a very fitting favorite word for Alessio Fasano, MD, professor of pediatrics, medicine, and physiology at the University of Maryland School of Medicine, medical director of the Center for Celiac Research, and director of the Mucosal Biology Research Center, both in the School of Medicine. It's the word he uses to describe how his failed search for a cholera vaccine led to one of the University's most exciting—and ongoing—success stories in the field of translational research and commercial partnerships.

Discoveries from Fasano's lab in the 1990s and early 2000s led to the startup and accelerated success of Alba Therapeutics Corp., a privately held, clinical-stage biopharmaceutical company founded in 2004 by Blake Paterson, MD, with key participation by Fasano. Alba, which is located in the University of Maryland BioPark, focuses on the discovery, development, and commercialization of protein therapeutics to treat autoimmune, immune-mediated, and inflammatory diseases.

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Clinical trials currently under way include two Phase IIb studies of larazotide acetate (AT-1001) in the treatment of celiac disease (CD). Safety studies of the drug with healthy volunteers and volunteers with CD have already been successfully completed.

When people suffering from the genetic disorder ingest gluten, a mixture of proteins found in wheat and other grains, an autoimmune reaction takes place that can damage the small intestine. In 2003, Fasano's team undertook the largest epidemiological study in U.S. history, screening 13,000 people from 35 states for CD. The results astounded the health care community; current statistics show that one in 133 people nationwide suffers from CD.

The Food and Drug Administration granted a "fast track" designation for larazotide acetate, and Alba Therapeutics now employs 45 people, has received more than \$40 million in financing, and in 2007 entered into a \$325 million strategic partnership with Shire Pharmaceuticals, a fast-growing global specialty biopharmaceutical company listed on the London, NASDAQ, and Toronto exchanges.

With trial results anticipated later this year, Alba is poised to become an even bigger player in the competitive world of enterprise pharmaceuticals. But current head of Alba, Bruce Peacock, who replaced Paterson as CEO in April 2008, echoes the driving philosophy of University researchers and Alba Therapeutics. "It's not just about making a buck, it's about making a difference," says Peacock.

And drugs developed based on the discoveries made in Fasano's lab could make a big difference. Although the trials currently under way are focused on CD, the application of the discoveries and technologies developed by Fasano and Paterson have potentially broad applications in the treatment of other autoimmune diseases, including type I diabetes, rheumatoid arthritis, multiple sclerosis, and others.

"This is as translational as it gets," says Fasano, who in 1990 came from Naples, Italy, to the University of Maryland School of Medicine's Center for Vaccine Development (CVD) to study the causes of acute and chronic diarrhea. "I came to the CVD because it was the best place in the world to learn about bacterial pathogenesis," says Fasano. His three-month scholarship became a two-year research project when, "We had the unbelievable luck to discover many, many toxins produced by bacteria in the gut." In 1993, at the age of 37, Fasano founded the Division of Pediatric Gastroenterology and Nutrition at the School of Medicine, where he still treats patients.

Another strong driving force behind the founding of Alba was the desire of both Fasano and Paterson to alleviate the suffering of their patients. Fasano was determined to find a way to help the young patients that he saw with what seemed to be chronic gastrointestinal problems when he stumbled on one of the best-kept public health secrets of the last century—the prevalence of CD among the American population. That in turn led to years of research to unlock the mysteries of the mechanisms that trigger CD and other autoimmune diseases.

"In Dr. Fasano, we have not only a skilled scientist drilling away at the biological mechanisms that cause and facilitate disease. We also have a compassionate clinician working to alleviate the pain and distress of his patients. He sees disease at every point on the spectrum, and the broad perspective he brings to his understanding of human health and disease is invaluable to his work and to the University of Maryland School of Medicine," says E. Albert Reece, MD, PhD, MBA, vice president for medical affairs, University of Maryland, the John Z. and Akiko K. Bowers Distinguished Professor, and dean of the School of Medicine.

"Serendipity has played a key role in the evolution of my study of CD—and also in the search for its cure," says Fasano. In the late 1980s, he was working on a new vaccine for cholera. When the failed vaccine provoked enough diarrhea to render it clinically unacceptable, "Our years of hard work were literally down the toilet," says Fasano. "At that point, we could give up and move on to another project or try to understand what went wrong. We chose the latter, and this act of serendipity—the design of nature that overcomes our plans—led us to discover a new toxin in vibrio that caused diarrhea by another mechanism."

In 2000, Fasano and his colleagues discovered the protein zonulin, which regulates the impermeability of the intestine. When zonulin moves past the natural barriers of the intestine—and the tight junctions (areas between cells) open—it can trigger an autoimmune response, such as the unfavorable intestinal reaction that occurs in celiac patients. Fasano and his researchers discovered that people suffering from CD had zonulin levels 10 times higher than normal.

Taking the discoveries from Fasano's lab, the University's Office of Research and Development (ORD) established a strong portfolio with more than 100 patents and began shopping the contents to potential partners. And serendipity—another lucky accident—led to the meeting of Alessio Fasano and Blake Paterson.

A critical care doctor trained at Harvard and Massachusetts General Hospital, Paterson practiced anesthesiology in the cardiothoracic and pulmonary arena. In 1991, he launched a company that manufactured a small health device. After he sold the successful company seven years later, he worked in drug development and commercialization for several of the largest pharmaceutical companies in the world, and in 2003 he approached the University of Maryland, Baltimore (UMB)—but not because of Fasano’s discoveries.

“For me, it was a serendipitous discovery of Alessio’s work,” says Paterson. “I’m on the board of directors for the Interstitial Cystitis Foundation, a patient advocacy organization. I was meeting with Susan Keay [professor of medicine in the School of Medicine] to look at developing a diagnostic tool for this chronic and painful bladder disorder.”

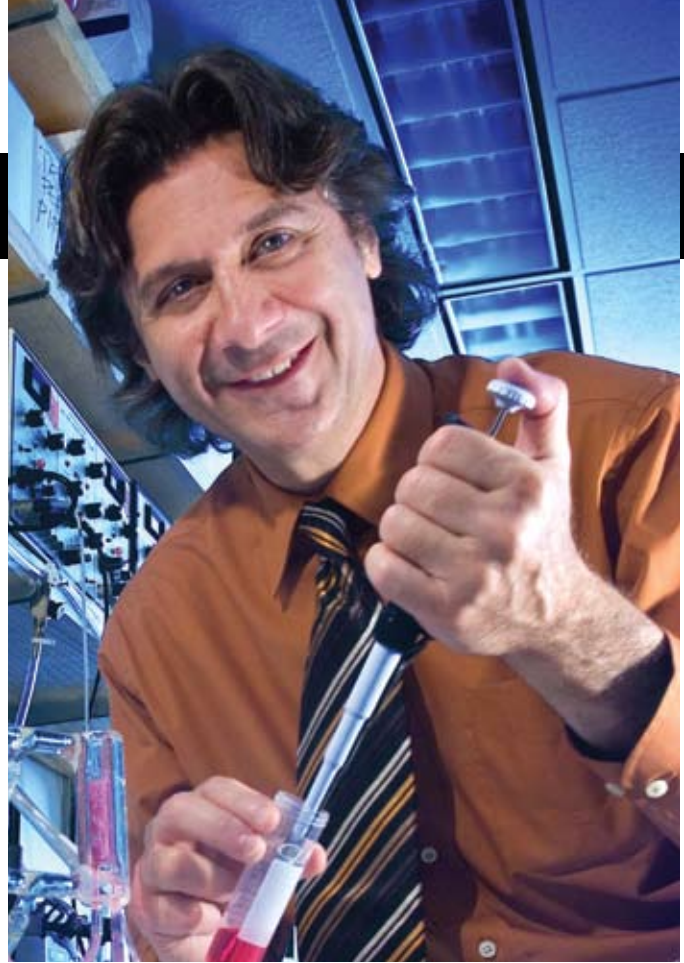
While reading about technology development at UMB, Paterson came across Fasano’s technology portfolio and became intrigued. “At that time, we thought the barriers between tissues and spacing between cells were closed—like cement. Alessio’s group was proposing something different—that the openings [the tight junctions] could be regulated,” says Paterson.

He notes that before the discoveries in Fasano’s lab, loss of barrier function was treated as a result of the autoimmune disease, not as a cause. “Our work turned that precept on its head—it is the consumption of gluten that causes the trigger that makes the tight junctions open, resulting in an increase of zonulin and the ‘leaky gut’ so often found in celiacs,” says Paterson.

“The conventional thought is to open barriers to get a vaccine into the body to treat the autoimmune disorders. Nobody thought you could block the leak that is the component of so many autoimmune diseases. We did a 180-degree turn and developed a drug to keep those barriers from opening. This is translational medicine at its best—figuring out how to make a drug to keep people from getting sick,” says Paterson.

After founding Alba, Paterson raised \$1.6 million in seed funding, receiving early support from the Maryland Industrial Partnerships Program and the Maryland Technology Development Corporation. In 2006, Fasano and Paterson went on the road to raise the major capital needed to build a biotechnology company, received \$30 million in Series A financing and moved into the University of Maryland BioPark with support from Maryland’s Department of Business and Economic Development.

Finding entrepreneurial partners like Blake Paterson is an integral part of the mission of UMB’s Office of Research and



ALESSIO FASANO

Development. “We try to match each technology with the right entrepreneur,” says James L. Hughes, MBA, vice president of ORD. “The entrepreneur needs to be smart, creative, and experienced, but he or she also needs to be committed to overcoming the inevitable setbacks that occur in bringing any new idea to fruition.”

Fasano and Paterson both give University President David J. Ramsay, DM, DPhil, enormous credit for promoting biotechnology and translational research, not just at UMB, but also in the state of Maryland. “His vision and dedication has been remarkable. Few people can claim more credit than he can for what he has done for biotechnology in the state of Maryland,” says Paterson.

And at the biotechnology park first envisioned by President Ramsay many years ago, Alba researchers are eagerly awaiting the results later this year of the clinical trials that might promise some relief for CD sufferers. But no matter what the outcome, says Alba CEO Peacock, his team will continue to look for solutions to the treatment of CD and other autoimmune diseases.

Likewise, under Fasano’s leadership, the Center for Celiac Research is using donations to provide crucial information in support of Alba’s clinical trials and to achieve other breakthroughs in treating patients with celiac disease.

To learn more, visit [www.albatherapeutics.com](http://www.albatherapeutics.com) and <http://celiaccenter.org>.