WHO/PAHO helps the world combat mental illness

By Rosalia Scalia

Mental and behavioral disorders cause enormous suffering, altering the lives of people throughout the world. By 2010, the number of people suffering from mental disorders, such as depression and schizophrenia, in the Western Hemisphere is expected to reach 176 million.

Two of the international public health organizations that reported those statistics, the Pan American Health Organization (PAHO) and the World Health Organization (WHO), have joined forces with the School of Nursing to tackle the problem head-on. PAHO, which works to improve health and living standards in countries throughout the Americas, is a region of WHO, the public health arm of the United Nations.

To help combat mental disorders, the School of Nursing was named the first WHO/PAHO Collaborating Center for Mental Health Nursing in July 2002.

The center focuses on mental health nursing through education, training information, and research projects that involve interdisciplinary collaborations with institutions in Central and South America. The designation allows the School to create specific projects that address mental health treatments and quality care initiatives and to raise funds to implement them.

"We are extremely honored to have the only WHO/PAHO Collaborating Center in the nation, which focuses specifically on mental health nursing, housed within our School," says Janet Allan, PhD, RN, CS, FAAN, dean of the School of Nursing.

"This collaborative effort with our colleagues in Latin and Central America, the Caribbean, and Mexico, will strengthen the knowledge base of mental health nursing and practice, and offer opportunities for faculty and student involvement in a variety of exciting initiatives," adds Allan.

Susanna Nemes, PhD, associate professor in the School of Nursing, was named the center's new director during the summer of 2005. She previously worked as vice president of tobacco, drugs, and alcohol research at Danya International, Inc., a health communications and technology firm in Silver Spring, Md., and as adjunct assistant professor at George Mason University College of Nursing and Health Sciences. From 1994 to 1999, Nemes worked as project director at the Center for Substance Abuse Research at the University of Maryland, College Park.

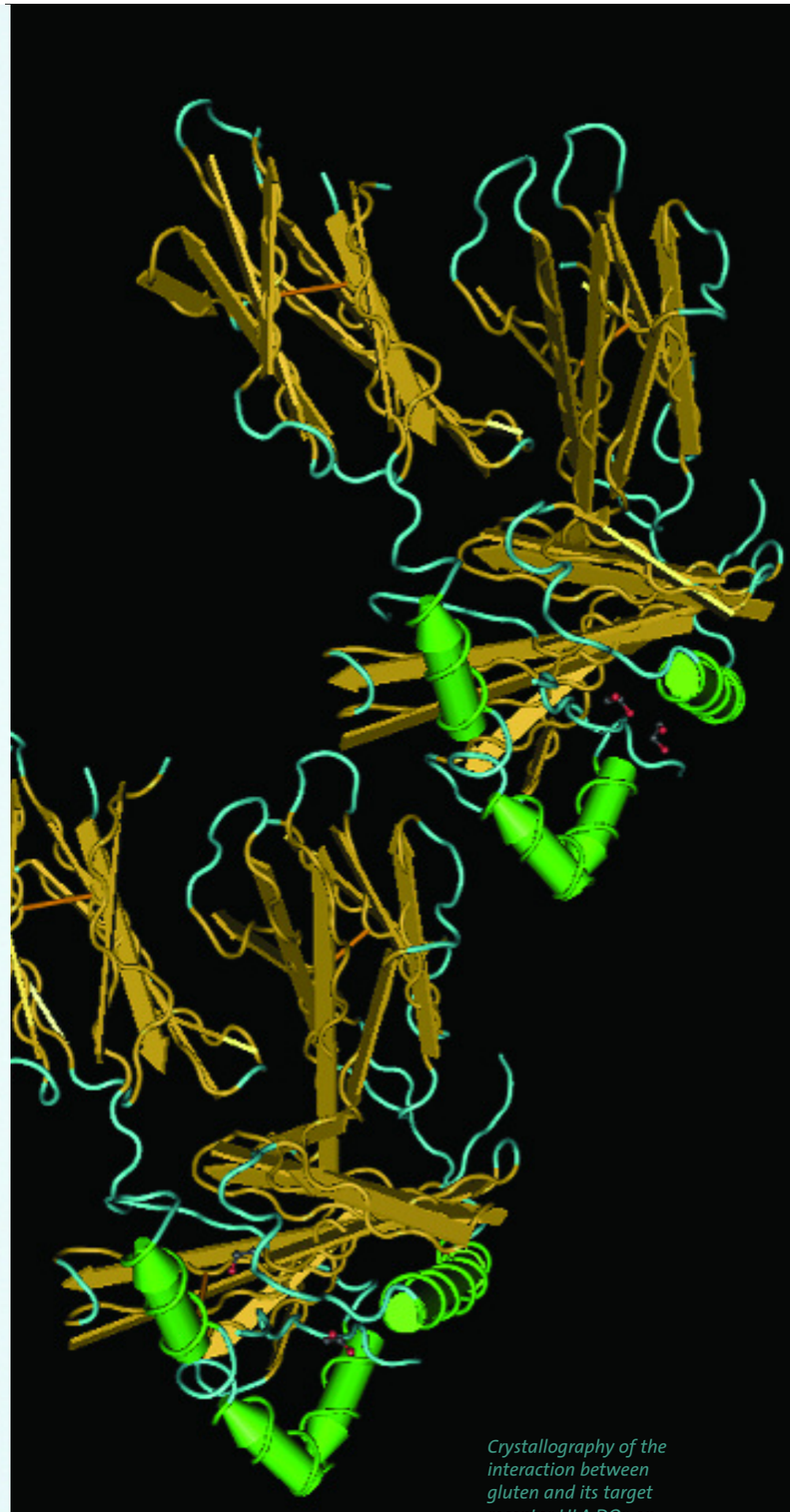
"We look forward to having an impact in mental health care in the Americas and Caribbean by conducting research and building capacity in areas where it is needed," Nemes says. "In order to accomplish this, we will be teaming with other WHO/PAHO colllaborating centers, as well as departments within the University of Maryland, Baltimore. This will allow us to share resources and expertise in working with mental health issues around the world."

According to Sally Raphel, MS, APRN/PMH, FAAN, deputy director of the center, the School hopes to advance three collaborative projects focusing on research, education, and practice. For instance, a project with the International Society of Psychiatric Nurses; Sigma Theta Tau International; the University of Alberta, Canada; and Georgetown University involves a partnership with the University of Panama School of Nursing. The project's aim is to train mental health workers, including nurses, according to local needs, and create best practices that offer safe and effective nursing services.

Also in the planning stage is a project that focuses on reducing the number of adolescents at risk for HIV infection in Puerto Rico in partnership with the University of Turnado, Puerto Rico.

Another important goal has been the development of teaching guidelines for mental health nursing for consistent practice at the baccalaureate or basic level.

The center has also developed databases of mental health programs and nurse experts in the WHO/PAHO region to create a unified nursing information system among countries and boost educational opportunities.



Crystallography of the interaction between gluten and its target receptor HLA DQ2 on antigen-presenting cells.

Mucosal Biology Research Center Searches for Cures to Autoimmune Diseases

By Randolph Fillmore

Pediatric gastroenterologist and professor in the School of Medicine, Alessio Fasano, MD, made scientific history with his colleagues in 2000. They discovered an important protein named "zonulin" that regulates the permeability of the intestine. The scientists determined that when zonulin travels past the natural barriers in the intestine it can trigger an autoimmune response that appears to contribute to a number of diseases, such as celiac disease and possibly Type 1 diabetes (T1D), multiple sclerosis, and rheumatoid arthritis.

The discovery, as with most scientific discoveries, was built on earlier findings. In the late 1980s, "tight junctions," previously unknown areas between cells, were discovered. In the early 1990s, the discovery of the bacterial protein *zonula occludens toxin* (ZOT) was destined to change future biomedical research. ZOT was found to play a role in opening tight junctions, which then allowed toxins to cross nature's intestinal barriers with the potential to cause disease.

Fasano, whose career was devoted to solving biological puzzles related to gastrointestinal diseases, and not necessarily to autoimmunity, confesses that he was not looking for zonulin throughout most of his career. In the early 1990s, he was trying to help make an effective vaccine for cholera using a live, attenuated cholera virus. "I failed," says Fasano.

Although preventing cholera would not be one of his victories, his interest in celiac

disease, coupled with the zonulin discovery, provided an enormous breakthrough, both for Fasano and those suffering from the intestinal disorder.

Celiac disease is a digestive and autoimmune disorder that causes damage to the lining of the small intestine when foods containing gluten are consumed by individuals who are allergic to gluten. As a result of the damage, people with celiac disease are unable to absorb nutrients normally and can suffer from a range of debilitating symptoms and both intestinal and extra-intestinal problems.

Undaunted by his apparent failure with cholera, Fasano continued following his interest in celiac disease. "It did not make sense that something as complex as the cell machinery targeted by ZOT was there just to make people sick," reasoned Fasano.

When he applied his newly found knowledge of ZOT and zonulin to what he knew about celiac disease, he found that persons suffering from that disorder had zonulin levels 10 times higher than normal. Fasano postulated that zonulin had something to do with opening the tight junctions in nature's mucosal barrier, allowing gluten to pass through.

"We know that the trigger for celiac disease is the gluten that gets past the mucosal barrier," observes Fasano. "We do not know what trigger causes multiple sclerosis, rheumatoid arthritis, or Type 1 diabetes. Once we learn what the trigger is for those autoimmune diseases, we will be well on the way to curing them."

Another significant development in Fasano's lab could also lead to a cure for T1D. Researchers investigated the role of the intestinal tight junction modulator zonulin in animals prone to T1D and concluded that blocking the zonulin receptor reduced the incidence of T1D by 70 percent. Their findings, published in the February 2005 proceedings of the National Academy of Science, suggest that inhibiting the zonulin system may be an innovative therapeutic tool to prevent or treat T1D.

"When we took intestinal permeability out of the picture, we found we could prevent T1D or reverse it in our animal models," says Fasano.

Today, thanks in large part to the discovery of zonulin and its implications, Fasano heads one of the newest centers at UMB, the Mucosal Biology Research Center (MBRC). Opened in June 2004 in Health Sciences Facility II, the MBRC is a collaborative hub for campus researchers and clinicians.

Formal and informal collaborations at the MBRC advance research.

"The mission of the MBRC is to serve as a multidisciplinary research center aimed at understanding the molecular basis for human diseases of the gastrointestinal and respiratory tracts, the two systems accounting for 99 percent of our interface with the environment," says Fasano.

"We are also actively engaged in joint ventures in translational research with innovative biotechnology and pharmaceutical companies. We want to get the fruits of our labor—whether newly developed novel drugs, new models of human diseases, new therapies and new drug delivery systems—to the patients who need them."

Fasano is the first to note that these goals cannot be realized without extensive collaboration with scientists in other areas of study, and with partners from industry.

"The MBRC is comprised of 33 faculty members from the University of Maryland as well as adjunct members in associated academic and biotechnology centers," explains Fasano.

One of Fasano's closest collaborators is James Nataro, MD, PhD, a professor of pediatrics and medicine in the Center for Vaccine Development in the Division of Infectious Diseases and Tropical Pediatrics.

"We need a close interface between academia and industry. We are not here to make money. We're here to make people better," says Fasano.

"Dr. Fasano and I have been working together for over 10 years," says Nataro. "For most of that time we have worked closely to discover and characterize bacterial enterotoxins—proteins secreted by bacteria that cause diarrhea in the human intestine. Most recently, we have been working on investigations related to the importance of regulating the permeability of the gut."

Nataro calls their collaborations "most productive" and the reason why ZOT, tight junctions, and zonulin are now part of the dialogue and investigations in his lab. But what does that collaboration involve?

"Sometimes it means going out for a beer, or sitting together at a meeting," says Nataro, who adds that successful collaborations require "fertility factors" and the cross-fertilization of ideas. "You talk about your observations and findings and help each other make sense of them."

Fertility factors help create those rewarding "eureka moments," says Nataro. "In theory, collaboration is talking to everyone, as if we were in an enormous chat room," says Nataro.

Formal campus collaborations with the MBRC include the Center for Vaccine Development, the Marlene and Stewart Greenebaum Cancer Center, the Baltimore Veterans Affairs Medical Center, the Institute for Human Virology, the University of Maryland General Clinical Research Center, and the Center for Celiac Research (CFCR).

"The Center for Celiac Research has been around since 1996," notes Pam King, CFCR's director of operations. "When the MBRC opened in 2004, we came under their umbrella."

Beyond academic circles, it is only through collaboration with industry that innovations born in academia will eventually get to the bedside of the patient, states Fasano.

"Academia is the right environment in which to test and prove a concept, but we have few resources and cannot take the financial risk involved in getting a product to market," he says. "We need a close interface between academia and industry. We are not here to make money. We're here to make people better."

Collaboration between the MBRC and industry has expanded with the partnership between the MBRC and the Baltimore-based start-up, Alba Therapeutics Corp. Formed in 2004 and headed by co-founder and Chief Executive Officer Blake Paterson, MD, Alba Therapeutics is working with the MBRC to develop drug applications based on recent discoveries about zonulin and its functions. Co-founder Fasano serves as interim chief scientific officer.

The goal, according to Paterson, is to control the opening and closing of the tight junctions. That control will allow either for drugs to be delivered into the body with the help of zonulin analogues or to develop therapies to help keep tight junctions closed, thereby preventing the inordinate entry of antigens into the body.

"This represents a radical departure from most approaches to autoimmune therapy that focus on immune suppression rather than blocking the triggers for these diseases," explains Paterson. "The remarkable potential of blocking the zonulin pathway to treat autoimmunity lies in the fact that the identification of the autoimmune trigger is immaterial. As long as zonulin causes the barrier leak and is responsible for the passage of the trigger, we can stop the autoimmune process dead in its tracks by re-establishing the integrity of that particular barrier."

Consequently, the company is focusing its efforts on developing a blocker to help prevent celiac disease and T1D, which are known to be associated with a "leaky gut." It is a condition that serves as a likely portal of entry for the disease triggers, says Fasano.

"By gaining the ability to manipulate the zonulin pathway, we may have a key to treating autoimmunity," says Paterson, a former executive with Eli Lilly and Company.

According to Paterson, Alba Therapeutics' management team is experienced in peptide discovery, drug development, and commercialization. With a combined experience of more than 100 years in industry, team members have developed approximately 10 therapeutic macromolecules, 10 small molecule pharmaceuticals, and have launched 10 new drug products.

To support its efforts to expedite clinical trials of its leading zonulin antagonist, AT-1001, Alba Therapeutics has launched a fundraising campaign.

"Developing and registering a drug usually takes 10 years and hundreds of millions of dollars," states Paterson. "Our challenge is to get this done in half the time and for a fraction of the cost."

Fasano adds, "Our advantage is that we have developed a new model for autoimmune diseases that depends on three elements: a genetic predisposition, a trigger, and an intestinal barrier that has lost its protective function," says Fasano. "The ability to prevent celiac disease by eliminating the trigger gluten has become a reality. The utility in restoring the lost intestinal barrier in animal models to prevent or reverse T1D has been demonstrated in the lab."

So what's left for Fasano and his colleagues to discover?

"What we don't have is the trigger that causes multiple sclerosis, rheumatoid arthritis, or T1D," he says. "Through our collaborations with scientists and clinicians with expertise in cell biology, mucosal immunology, infectious diseases, inflammatory processes, drug and antigen delivery, and trauma and wound repair, we stand to make great strides.

"We need to determine whether manipulation of mucosal barriers may prevent the interplay between those triggers and the immune system of people genetically susceptible to develop autoimmunity. That is the key to finding a cure for these devastating diseases. With all that needs to be done, it amazes me how far we have come in just a year and a half," says Fasano.

www.medschool.umaryland.edu/mbrc

Researchers at the MBRC investigate the molecular basis for gastrointestinal and respiratory disease.

PHOTOGRAPHS BY MARK TESKE