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BioMarketing Insight Newsletter

Creating Markets and Marketing Strategies

Dear Regina,

Welcome to BioMarketing Insight's monthly newsletter.

Last month I covered Cancer Vaccines - Tricking the Immune System. If you missed last month's article, click here to read it. This month is part 2 of a two-part series on the immune system. I'll discuss how a leaky gut and maintaining gut microbiome influences our immune system.

Read on to learn more about this topic and other current news. On the right are quick links to the topics covered in this month's newsletter. The next newsletter will be published on August 15th.

We encourage you to share this newsletter with your colleagues by using the social media icons at the top left, or by simply forwarding the newsletter via email.

Please email me, Regina Au, if you have any questions, comments, or suggestions.

Sincerely,
Regina Au
Principal, Strategic Marketing Consultant
BioMarketing Insight

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Regenerative Medicine - A New Dimension

I am pleased to announce that my article on 3D printing and how it has influenced and advanced regenerative medicine and beyond was published in the April 2014 issue of European BioPharmaceutical Review (EBR). If you have not had a chance to read my article, click here. For more information on EBR, click here .

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Save the Date: POC+mHealth Diagnostic Summit - November 5 - 7, 2014

Amidst a diminishing supply of providers and escalating costs of healthcare, the call for new point-of-care testing, direct-to-consumer diagnostics, patient-centered devices and apps to support mobile healthcare has never been greater. These technologies offer clinicians decision support capabilities, healthcare systems a real-time data stream for population health management, and they offer providers, patients and payers the chance to improve the outcome of care for less expense.

The conference will cover the topics technology developers, clinicians, researchers, payers and innovators should consider when developing, launching and integrating new point-of-care testing, patient-centered devices, direct-to-consumer diagnostics and apps/devices to support mobile healthcare.

I will be speaking on Friday, November 7th at 9:30 am on "eMedicine, eMonitoring, eHospital, and mHealth Apps: Seven Critical Factors that Need to Be Assessed in Determining Whether Your Product Will Be Commercially Successful." To learn more about Point-of-Care and Mobile Health Diagnostics Clinical-Consumer Interface presentations, click here. To view the entire agenda, click here. To register, click here.

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How a Leaky Gut and Our Gut Microbiome Influence Our Immune System

What does a leaky gut, and our gut microbiome, have to do with our immune system? Scientists are discovering that it has **a lot** to do with how well our immune system works.

What is the definition of a leaky gut, or intestinal permeability? Here are some comments from gastroenterologists from one source. "Leaky gut syndrome" is denoted by symptoms that include bloating, gas, cramps, food sensitivities, and aches and pains. But we don't know what causes this syndrome.

"From an MD's standpoint, it's a very gray area," says gastroenterologist Donald Kirby, MD, director of the Center for Human Nutrition at the Cleveland Clinic. "Physicians don't know enough about the gut, which is our biggest immune system organ."

"Leaky gut syndrome" isn't a diagnosis taught in medical school. Instead, "leaky gut really means you've got a diagnosis that still needs to be made," Kirby says. "You hope that your doctor is a good-enough Sherlock Holmes, but sometimes it is very hard to make a diagnosis."

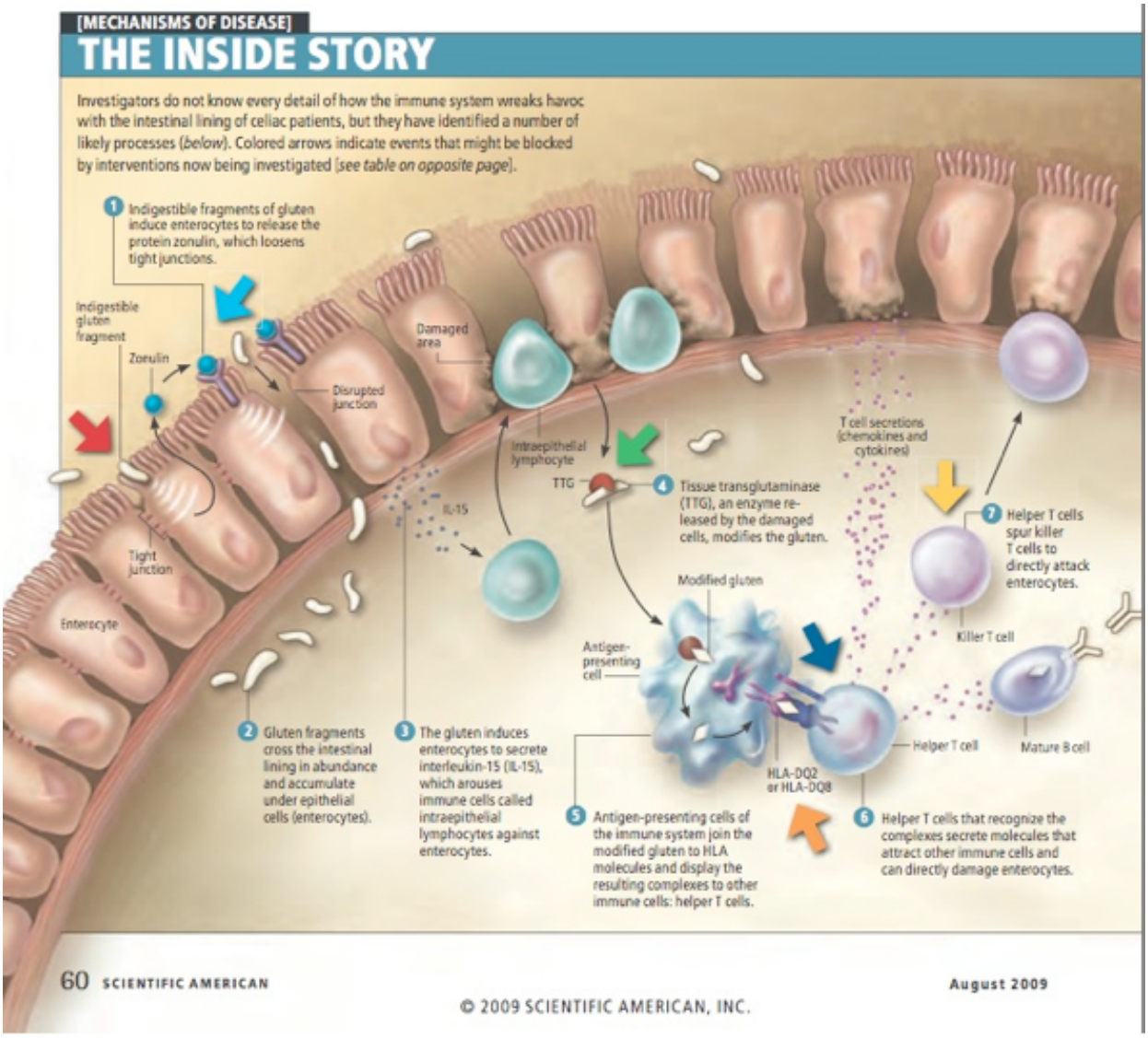
"We don't know a lot but we know that it exists," says Linda A. Lee, MD, a gastroenterologist and director of the Johns Hopkins Integrative Medicine and Digestive Center. "In the absence of evidence, we don't know what it means or what therapies can directly address it."

Our intestines have a very thin lining that prevents substances other than nutrients to pass into our blood stream. Intestinal permeability is when the tight junctions (TJs) in the intestinal lining that control what passes through don't work properly and substances leak into the bloodstream. Imagine the tight junctions as doors and something is making the doors open to allow substances that normally don't pass through to pass through.

The gastrointestinal tract "together with the gut-associated lymphoid tissue and the neuroendocrine network, the intestinal epithelial barrier, with its intercellular tight junctions, controls the equilibrium between tolerance and immunity to non-self antigens," according to Dr. Alessio Fasano's paper on "Zonulin and Its Regulation of Intestinal Barrier Function: The Biological Door to Inflammation, Autoimmunity, and Cancer."

Dr. Fasano, of Massachusetts General Hospital, discovered the protein zonulin, "the only physiological modulator of intercellular tight junctions described so far that is involved in trafficking of macromolecules and, therefore, in tolerance/immune response balance." He is the foremost expert on gluten and Celiac Disease.

You may be thinking, I don't have Celiac Disease, so what does this have to do with me? Gluten is the culprit. Why? Gluten, genetically modified (GM) in wheat has an unusual composition that cannot be completely digested. Gluten has too many proline and glutamine amino acids and our enzymes do not recognize this sequence. The same can be said for GM barley and rye, said Dr. Fasano during his talk at the Gluten Summit. Gluten is comprised of two main proteins, gliadins and glutenins, and both are toxic for Celiac Disease patients. Gliadins triggers the release of zonulin, which opens up the TJ, or doors, and allows gliadins and sometimes other molecules, to pass through. When gliadins are seen, it triggers an immune response, which leads to inflammation.



Since gluten can not be completely digested, zonulin is released loosing the tight junctions (TJs) of the intestinal wall. When gluten passes through the intestinal wall into the blood stream, it triggers the immune system resulting in inflammation.
Source: *Scientific America, Inc.*.

When food molecules pass through, it triggers the immune system and one can form food sensitivities in response to these molecules. When immune cells pass through, they can travel anywhere in the body, said Dr. Fasano. If the immune cells reach the joints, they can cause joint pain. If they reach the nerves, they can cause peripheral neuropathy. If they reach the skin, they can cause dermatitis herpetiformis and so forth. One theory is that the TJ-- or doors-- may remain open longer than usual, thus allowing food molecules and immune cells to pass through, possibly due to an overproduction of zonulin. Scientists don't know why this happens, but in Celiac patients there is an up-regulation of zonulin in the acute phase "and that zonulin is released from intestinal mucosa following exposure to either gluten or microorganisms."

For many people, our immune system takes care of the gliadins and everything is fine. For others, depending on their genetic make-up or predisposition, the immune system goes awry. In Celiac patients, there is a miscommunication between the innate and the adaptive immune system and the adaptive immune system starts attacking its own cells, leading to gut damage. Since Celiac Disease is a genetic disorder, it is believed that these people have at least one of two genes needed to develop Celiac; HLA-DQ2 and HLA-DQ8. Dr. Fasano believes that these two genes act like "docking stations" for gluten when it has been changed by transgutaminase, which is the only way the immune system recognizes gluten as the enemy. Antigen-presenting cells (APC) present deliver or transport this

complex to T cells and T cells start producing cytokines that will be used against its own cells. In classic Celiac Disease the damage occurs in the intestine.

In gluten sensitivity, it exclusively involves the innate immune system and leads to inflammation and symptoms, but will never lead to enteropapthy, stated Fasano. Symptoms of non-Celiac gluten sensitivity include the following: abdominal pain, headaches, foggy mind, chronic fatigue and depression. These symptoms long-term can lead to poor quality of life and possibly shorter life expectancy.

According to Dr. Fasano's paper "Zonulin has been observed to be involved in intestinal innate immunity and to be up-regulated in several autoimmune diseases, including Celiac Disease (CD) and type 1 diabetes (T1D), in which TJ dysfunction seems to be the primary defect."

Dr. Fasano believes the gut is the most sophisticated immunological component in our body that is controlled by a neuroendocrine network. He believes our intestine is our interface with the environment. Information is exchanged in a highly controlled and coordinated manner. Our state of health or disease is the coordination of our genes and the environment and our "gut is the point of entry in which these two elements, they will meet."

Fasano believes that there has been an epidemic of autoimmune disease that has developed over the last 40-50 years. He said we can't blame genetic changes because genetic mutations take centuries to develop. We are unable to adapt to our fast changing environment. Our intestinal barriers function as a integral part of the equation, where specific genes control our gut permeability and the proteins or fragments that cross this barrier are the instigators that lead to autoimmunity.

"A fast-growing number of diseases are recognized to involve alterations in intestinal permeability related to changes in TJ competency. These comprise autoimmune diseases, including T1D, CD, multiple sclerosis, and rheumatoid arthritis, in which intestinal TJs allow the passage of antigens from the intestinal milieu, challenging the immune system to produce an immune response that can target any organ or tissue in genetically predisposed individuals. TJs are also involved in cancer development, infections, and allergies."

"Once gluten is removed from the diet, serum zonulin levels decrease, the intestine resumes its baseline barrier function, the autoantibody titers are normalized, the autoimmune process shuts off and, consequently, the intestinal damage (that represents the biological outcome of the autoimmune process) heals completely."

The composition of the bacteria in our gut is the key factor impacting intestinal physiology, where microbiome helps the intestinal immune function to maturity, stated Fasano. He said that 99% of the bacteria in the gut can't be cultured and that our microbiome is 100 times more complex genetically. Our microbiome affects how our genes are expressed. As humans, we have a rudimentary genetic make-up of 25,000 genes, compared to an earthworm, that has 90,000 genes. Our micrbiome is highly affected by our nutrition and environment and is impacted by pollution, chemicals and radiation. We are constantly exposed to antibiotics, not only from antibiotic usage, but also from the vegetable and animal products that we eat, the vast majority grown with the use of antibiotics.

Dr. Fasano's paper states " Enteric infections have been implicated in the pathogenesis of several pathological conditions, including allergic, autoimmune, and inflammatory diseases, by causing impairment of the intestinal barrier. We have generated evidence that small intestines exposed to enteric bacteria secreted zonulin..... This zonulin-driven opening of the paracellular pathway may represent a defensive mechanism which flushes out microorganisms so contributing to the innate immune response of the host against bacterial colonization of the small intestine."

Since the first paper detailing the human microflora, there has been an uptick in the interest of microbiome research in the past 10 years. There are currently five start-ups and there may be more that are focusing on this field:

1) **Seres Health**, founded by Flagship VentureLabs, is "developing Ecobiotic™ therapeutic products, the first therapeutics that catalyze a shift to health by augmenting the biology of the microbiome, " according to Flagship's website.
2) **Second Genome**, founded in 2010, secured a Series A deal with Janssen to advance new microbiome-based therapies for ulcerative colitis.
3) **Vedanta Biosciences**, founded by PureTech Ventures and a team of immunology and microbiology experts, is focused on developing microbiome modulators for autoimmune and inflammatory diseases.
4) **Microbiome Therapeutics**, previously known as NuMe, is running two clinical trials of a microbiome modulator designed to enhance insulin sensitivity in patients with prediabetes, and lessen adverse GI effects in those who are taking the antidiabetic drug metformin.
5) **ViThera Pharmaceuticals**, founded in 2009, is engineering bacteria to deliver therapies to the gut. Their lead program is in preclinical development for inflammatory bowel disease.

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Closing Thoughts

Our immune system is very complex and many factors -- genetics; properly functioning innate and adaptive immunity; an intestinal barrier impermeable to nutritional and environmental substances; and the microbiome -- all influence how well our immune system works.

Margaret (Peg) Riley, professor in the Dept. of Biology at UMass Amherst and cofounder of the Institute for Drug Resistance, has long been a proponent of microbes or microbiome. She stated in a presentation that our natural skin flora has a lot of microbes, yet we do not have an issue with infection. It's when our ecosystem is unbalanced that we encounter problems. Her theory is that we need more narrow spectrum antibiotics, because a broad spectrum antibiotics, also kill the good microbes and destroy the ecosystem.

Dr. Fasano stated the importance of microbiomes as a key factor impacting intestinal physiology and how our microbiome affects how our genes are expressed. People are now taking probiotics, which are good bacteria that maintain their microbiome and control any overgrowth of bad bacteria. Most probiotics have the following 4 genera: Lactobacillus, Bifidobacterium, Lactococcus and Pediococcus. Probiotic strains such as B. longum BB536, L. rhamnosus R0011 and L. helveticus R0052 have been clinically shown to have a positive influence on the composition of the intestinal microflora, promote intestinal health and support immune response.

I discussed how gluten leads to a leaky gut and how the immune system reacts depends on the individual. Unfortunately, gluten has another unfavorable effect, a glycemic index of 70 +, higher than any other natural food. This high glucose content causes glycation, where elevated blood sugar binds to protein. When this happens, free radical production increases and it damages everything in sight (DNA, fat, protein etc.), according to Dr. David Perlmutter, neurologist and associate professor at the University of Miami School of Medicine. This causes inflammation and is devastating to the human brain. But I am getting into another subject, a topic for another newsletter.

So stay tuned. Next month, I will discuss how gluten and glucose levels affect the brain and the heart.

If you are developing a product and have not conducted the business due diligence to determine commercial viability, email me for an appointment. For successful commercial adoption of your product, email me for an appointment.

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New Technology - Drug Resistance to Lung Cancer Drug Can Be Reversed

Scientists at Georgetown Lombardi Comprehensive Cancer Center and the National Cancer Institute have discovered why intrinsic resistance occurs in up to 40 percent of lung cancer patients who don't respond to erlotinib (Tarceva®), a targeted therapy designed to block tumor growth. They discovered a Src inhibitor, that could reverse it.

An over-expression of the growth protein Cripto-1 makes lung cancer cells resistant to the drug erlotinib (Tarceva®). Their findings were published in the Journal of Clinical Investigation. "Experiments in cell lines and in animals demonstrated that blocking Cripto-1 signaling transduction restored sensitivity to the drug, one of a number of EGFR inhibitors used in non-small cell lung carcinoma and other cancers."

A Src inhibitor was chosen, because Cripto-1 activates the oncogenic tyrosine-protein kinase Src. "This is a welcome finding because Cripto-1 belongs to a family of proteins that can be targeted by drugs that have already been developed," says the study's senior investigator, Giuseppe Giaccone, MD, PhD, associate director for clinical research at Georgetown Lombardi.

To read the full article in *World Pharma News*, click here.

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About BioMarketing Insight

We help companies de-risk their product development process by conducting the business due diligence to ensure that it is the right product for the right market and the market opportunity for the product meets the business goals of the company. We can then develop marketing strategies to drive adoption for the product.

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