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impact

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MOUSE MODELS: key to understanding celiac disease

Researchers at the Celiac Disease Center are renowned for developing mouse models of celiac disease. But what exactly are mouse models, and why are they so important? Mouse models are colonies of mice genetically engineered to develop a particular disease—to "model" that disease so scientists can study it.

Mice are excellent research subjects. Their organs and tissues are similar to those of humans. They carry virtually all the same genes as humans. They reproduce quickly, enabling scientists to breed multiple generations in short periods of time and study the differences between cohorts. And they are ideal for celiac research. Mice have the same immune responses as humans, and are easy to study as those responses evolve.

This is crucial in celiac research. "The development of this disease is a dynamic process," said Valerie Abadie, PhD, research assistant professor at the Celiac Disease Center and lead author of several papers on the center's mouse models. "You have several immunologic events that take place successively until a point where they induce tissue damage. You need to be able to monitor this immune response over a period of time to better understand what is the tipping point that causes the disease."

Moreover, mouse models enable researchers to study the immune response starting with the first-ever ingestion of gluten. This would be virtually impossible in humans. It is a rare person past infancy who has never ingested gluten and could eat it for the first time in a study. But mice in the lab can be raised completely gluten-free.

Abadie and her colleagues at the center have created several mouse models that have greatly advanced our understanding of celiac disease.

MODEL OF HLA-DQ8 PLUS IL-15

Researchers in Jabri's lab engineered these mice to have the DQ8 form of the Human Leukocyte Antigen (HLA) gene—one of the HLA types that predispose people to celiac disease—and also to overproduce interleukin-15 (IL-15), a cell-signaling molecule important to immune response. The team created this model to study the impact of IL-15 on celiac disease. Research in humans has shown that in people with celiac disease, the gut lining and the connective tissue between the finger-like villi in the intestines and the pouch-like spaces between them, called the lamina propria, produce abnormally large amounts of IL-15 in response to gluten.

IL-15 turned out to be crucial to this mouse model. After eating gluten, these IL-15-overproducing mice mounted an inflammatory immune response. This model showed for the first time that IL-15 is involved in the loss of oral tolerance to gluten.

But the mice did not go on to develop villous atrophy, the intestinal damage characteristic of celiac disease. Therefore, this was not a model of full-blown celiac disease. But it was a perfect model of "potential celiac disease," in which people

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Top : Valerie Abadie in lab.

Bottom : Students and technicians involved in studying cross-talk between different cell types using mouse models

Clockwise from left front: lab technician Jordan Ernest; graduate student Jordan Voisine; lab technician Amelia Davis; postdoctoral fellow Celine Meyer

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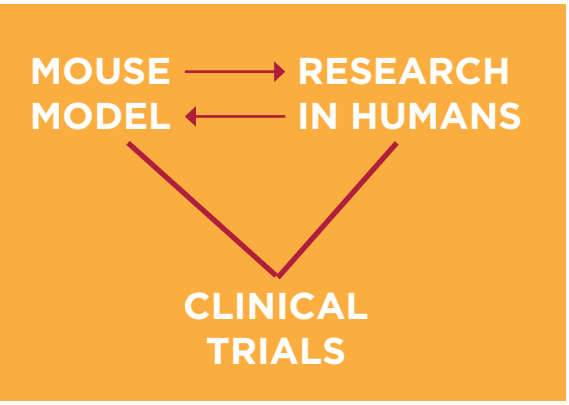

who are genetically susceptible to the disease have an immune response to gluten, but do not have villous atrophy. Further studying these mice, the scientists found that they overexpressed IL-15 everywhere in their bodies except the gut epithelium, the intestinal lining—a discovery that was to prove critical.

The team published a paper on this model in 2011. It pointed the way to the next step: developing a mouse model that developed intestinal damage.

THE WORLD'S FIRST ACCURATE MOUSE MODEL OF CELIAC DISEASE

A mouse model that develops intestinal damage from ingesting gluten—the central element of celiac disease—was the holy grail of celiac research. Developing one was a goal that eluded researchers worldwide for 20 years. Abadie and her colleagues in Jabri's lab solved the puzzle.

Their first mouse model had suggested that the gut epithelium played a critical role. The researchers explored this further in humans.

Using biopsies from endoscopies in UChicago Medicine patients, they compared the production of IL-15 and other biomarkers of stress in the gut epithelium in three groups: family members of celiac patients, people with potential celiac disease, and those with active disease.

Patients with full-blown celiac disease, including intestinal damage, overproduced IL-15 both in the gut epithelium and in the lamina propria. Family members and potential celiac disease patients, without intestinal damage, overproduced IL-15 either in the gut epithelium or in the lamina propria, respectively, but never in both intestinal compartments simultaneously.

Jabri hypothesized that a true mouse model of celiac disease would have to overexpress IL-15 in the epithelium—the one place the previous model did not overexpress it—as in the 75 percent of celiac disease patients who overproduce IL-15 in both the lamina propria and the epithelium.

The team engineered a model that did so. These mice have all the elements of celiac disease; they are genetically predisposed to it, they produce abnormally large amounts of IL-15 in both the gut epithelium and the lamina propria; and when they eat gluten they develop intestinal damage.

They are the first true mouse model of celiac disease.

The team published a paper on the model, with Abadie as the lead author, in the journal *Nature* in 2020. The lab is using the model to better understand how different cell types interact in the gut to cause tissue destruction. This mouse model only offers the opportunity to discover new therapeutic targets, but also to test them.

GERM-FREE MOUSE MODEL

The Jabri lab is now in the process of creating a germ-free mouse model of celiac disease—mice without a microbiome, the collection of microorganisms living in the gut.

Studies in humans have shown that people with celiac disease have different microbiomes from those without celiac. However, it is impossible to know if these differences are causes or consequences of the disease. With a germ-free mouse model, researchers could colonize mice with specific germs that have been isolated from patients and study their effect on the immune response to gluten without interference from other bacteria.

MODEL WITH HLA-DQ2 GENE

The team is also developing a mouse model with the HLA-DQ2 gene—a critical next step because this is the variant seen in 90 to 95 percent of people with celiac disease. "It's going to be an even better model, because there is a higher disease risk in patients carrying HLA-DQ2," Abadie said.

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Family's gift supports research examining gut-brain connection in celiac disease

After giving birth to her daughter, Catharon "Cat" Miller began noticing changes in her ability to focus.

"I'm a bit of a nerd, so I used a spreadsheet to track things like when my daughter slept and when we fed her," Miller said. "I remember one afternoon I was trying to read the spreadsheet, which was incredibly simple, and I couldn't do it."

Miller had the same difficulty when trying to comprehend other written materials, such as recipes or news articles. A business school graduate who was normally incredibly efficient and productive, Miller didn't feel like herself. Although she knew something was wrong, she couldn't pinpoint the root cause, so assumed it was simply the result of being a new mom.

It wasn't until two years later that Miller considered whether something she was eating might be affecting her ability to focus.

Thanks to family friends Laura Davis, inaugural chair of the newly formed Celiac Disease Center's Leadership Council, and Tony Davis, Miller learned about the University of Chicago Celiac Disease Center. After visiting the center, she was diagnosed with celiac disease, an autoimmune disease where the ingestion of gluten leads to damage in the small intestine.

Researchers at the Celiac Disease Center, including the center's director of research, Bana Jabri, MD, PhD, have long understood the acute physical symptoms of celiac disease, including nausea and abdominal pain after consuming gluten. But only recently have researchers begun to explore the disease's neurological and psychological impacts.

To further understanding of the gut-brain connection in celiac disease, Jabri is embarking on a new research project in collaboration with Jean Decety, PhD, Irving B. Harris Distinguished Service Professor in the Department of Psychology, and Sonia Kupfer, MD, associate professor of medicine. The first-of-its-kind study aims to determine if gluten ingestion causes the "brain fog" symptoms reported by Miller and other celiac patients. Such symptoms can range from the difficulty focusing that Miller described to anxiety, depression, irritability, poor sleep, and panic attacks.

Encouraged by the promise of this research, Cat and her husband, Brian Miller, a University of Chicago Medical Center trustee, donated $750,000 to advance the project.

"We are excited to support this foundational research, which will not only advance our understanding of the mechanisms underlying brain fog among celiac patients, but could also lead to larger studies and new therapies that target this at a neurological level," Brian said.

As the first broad, controlled study investigating how gluten exposure affects the brains of people with celiac disease, the study will evaluate patients who experience neurological symptoms following gluten exposure, as well as a control group of non-celiac patients.

Unlike other autoimmune diseases, where the trigger for symptoms is often unknown or involves a myriad of complex factors, the cause for celiac disease symptoms is clear—gluten ingestion—and therefore can be safely controlled in a research setting. Using Decety's expertise in functional magnetic resonance imaging (fMRI)—a non-invasive technique to examine the brain—study participants will undergo

BANA JABRI, MD, PHD

fMRI, blood testing, and psychological assessment before and after gluten ingestion.

"We are really lucky at the University of Chicago to have such strong relationships between clinicians and scientists across campus," Jabri said. "Together, we can design rigorous studies that leverage our cross-disciplinary expertise."

Based on mounting evidence, Jabri suspects that cytokines, small proteins released following gluten exposure in individuals with celiac disease, not only cause gastrointestinal distress but also lead to alterations in brain function. The study will determine if cytokine release is the culprit behind brain fog.

"It is a terrible experience for a patient with symptoms to be told that there is no explanation for it," Jabri said. "So just being able to tell patients they are not imagining these symptoms is going to really help people. But beyond that, I'm hoping that this initial study will seed many future studies, and help us understand brain fog

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from both a scientific and psychological perspective."

In addition to shedding light on gluten's impact on cognitive function among celiac patients, discoveries from this research study may offer insights into neurological issues reported by patients with a variety of conditions—from cancer to COVID-19 to other autoimmune diseases like inflammatory bowel disease and multiple sclerosis.

Beyond developing new treatments, Cat hopes the research will improve understanding and support for children and adults affected by celiac disease, along with people experiencing brain fog due to other conditions.

"Learning more about brain fog and being able to identify it as a demonstrable medical phenomenon will make many patients feel better and help them understand that they're not going crazy," Cat said. "It would be an incredible thing for there to be more understanding and acceptance around the psychological and emotional impacts of celiac disease, both for kids who are struggling in school after accidental gluten exposure and for adults facing challenges in the workplace."

Jabri is especially grateful to the Millers for their support.

"This is a perfect example of why philanthropy is needed to advance science," Jabri said. "If I went to the National Institutes of Health with this project tomorrow, there's no chance it would get funded because we don't yet have the preliminary data. Philanthropic funding is the driver that allows us to explore innovative ideas and opens the pathway for new research directions."

APR 17 CELIAC DISEASE & CONTINUUM OF CARE

HEAR FROM CELIAC DISEASE CENTER EXPERTS ON APRIL 17

All are welcome to the Celiac Disease Center's April 17 online symposium on "Celiac Disease and the Continuum of Care." The event, which provides Continuing Medical Education credits for healthcare professionals, is open to patients and families, too.

AMONG THE HIGHLIGHTS:

- **Vijaya Rao, MD, and Nutrition Advisor Lori Welstead, RD,** will discuss teens' transition to adult care
- **Director of Research Bana Jabri, MD, PhD,** will speak on the neurological symptoms known as brain fog
- **Tina Drossos, PhD, associate professor in the Department of Psychiatry and Behavioral Neuroscience,** will address the impact of celiac disease on the family
- **Katie O'Sullivan, MD**, will speak on type 1 diabetes and celiac disease

Other talks will cover supporting children's social and emotional development, and the future of celiac therapies. The agenda includes Q and As and panel discussions.

The symposium will run from 8:30 a.m. to 1 p.m.
For more information visit **cureceliacdisease.org/events/continuumofcare/**

To register visit, **https://cvent.me/BQr12a**

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FROM OUR DIETITIANS

By Vicki Gainsberg

CELIAC DISEASE 20 YEARS AGO: dietitian Vicki Gainsberg describes her journey

The dietitians who work with our patients are celiac disease experts, but some are also celiac disease patients. Vicki Gainsberg, RD, LDN, has to follow the same gluten-free diet as the children and adolescents who are her patients. Here she talks about her own journey, which began in another celiac disease world.

I was diagnosed over 20 years ago, in 1999; I was in my mid-twenties. I had gone traveling through Europe with some friends after finishing my undergrad degree at the University of Illinois at Urbana/Champaign. We backpacked for eight weeks. When I came back, I started having really bad GI symptoms—chronic diarrhea.

I thought maybe I picked up a bug in Europe. I saw my doctor; she said that's what it probably was. But it never went away. I went to GI specialists, including one who did a colonoscopy. They couldn't figure it out. Irritable bowel, they said; nothing major, just chronic diarrhea. I was anemic, but they did not correlate it with celiac disease.

So I lived my life and was miserable for a few years, not knowing what was going on. I lost a lot of weight. People thought I was anorexic. I was very, very thin. And I would eat like crazy. I wasn't absorbing anything. Everything I ate would go right through me.

Finally, I said, "I need a new set of eyes." I went to a primary care doctor who said, "Let's test you for celiac." They did the blood test; it came back positive.

It had taken four years.

I told my GI doctor; he said, "Oh, gosh, this is very rare. " He did a biopsy; it was positive. He told me to go on a gluten-free diet.

I was a dietitian at that point. I had just finished my internship at Loyola University Chicago. So I did my own research.

There was almost nothing gluten-free out there. The few options were like eating cardboard. I just ate a lot of naturally gluten-free foods. And eating out was a struggle. No one knew what gluten-free was.

A little later, I got involved in a support group. I taught gluten-free cooking classes at a Whole Foods kitchen. It was free. I would just make fun recipes. People loved it.

Things evolved over time. There are great products out there now, and so much awareness. But there's a lot of bad stuff out there, too.

A lot of gluten-free products are unhealthy. They have higher carbs, more fat, more sugar, which are added to try to improve the taste.

Today I have one child with celiac disease and one without it. My husband doesn't have celiac disease, but our house is completely gluten-free. When I go to the grocery, I shop the perimeter. That's where all the healthy food its. The mainstays of my grocery cart are fruits, veggies, dairy, eggs, meat, and fish. It's all gluten free

With my experience, I've always had an interest in gastrointestinal illness. I love to help anyone with celiac disease. Since my diagnosis, it's been a passion of mine.

I work with children and adolescents, up to age 18. With young children, I work more with the parents. Sometimes it's really hard when kids are diagnosed. Parents want to know, what do I give my child to eat? But by 6, 7, or 8 years old, kids understand. I always want them there with their parents.

Teens have specific needs. They put on a lot of weight once they're on the gluten-free diet; they're finally absorbing nutrients. That happened to me; within a year, I had gained all my weight back.

And they are concerned about going out with friends. They're embarrassed to ask at a restaurant—this was before COVID—how the food is prepared. I tell them to call ahead. And that your friends probably don't care that you're gluten-free.

I tell them, "This is important, but it's not who you are as a person. This is not your identity. That's not about what you can or can't eat."

I try to educate my patients on a well-balanced diet. I focus on the positive. When you take things out of your diet, you crave them even more. But I talk about what we can have in our diet.

I work with patients with all gastrointestinal conditions. But celiac is my favorite—because I live it every day.