

impact

FEB | 2018

THE ROLE OF VIRUSES IN CELIAC DISEASE:

A Q&A We Can All Understand

Nearly a year ago, a team of researchers and physicians from the University of Chicago, under the supervision of Dr. Bana Jabri, our Center's director of research, published a paper in the high impact journal *Science*, that received a great deal of acclaim and interest. The project was driven mainly by Romain Bouziat and Reinhard Hinterleitner, two post-doctoral researchers, along with the contribution of several lab members including Toufic Mayassi, Marlies Meisel, Sangman M. Kim and Valentina Discepolo, but also with the collaboration of other institutions, especially the group of Dr. Terence Dermody, expert pediatric virologist at Nashville, now at UPMC in Pittsburgh.

Here, Dr. Discepolo, MD, PhD, working as a visiting researcher in our celiac research lab, dissects it for us, explaining why it was truly important.

Q: Why is it significant that this paper was published in *Science*?

A: It is extremely significant that this

paper was published in *Science*, rather than in a medical or gastroenterology journal. *Science* contains articles about all science, from astronomy to zoology. So the fact that the editors were interested in an article about celiac disease tells us that the topic, the contribution of viral infections to the induction of autoimmune disorders, has far-reaching implications and has the potential for a much wider audience than merely those with an interest in celiac disease.

Reovirus, a virus that is normally rather innocuous, **can actually imprint a different response to food in the intestine.**

Q: Can you explain in laymen's terms what this paper showed?

A: Sure. This paper explains how we can finally see that reovirus, a virus that is normally rather innocuous, can actually imprint a different response to food in the intestine. For the first time we were able to dissect the mechanism by which a virus, which is an environmental trigger, can alter

the immune system selectively in the intestine in a way in which it is able to imprint a different response of the immune system to a food protein, which is something that has never been proven mechanistically.

Q: Please go through the process with me. Someone gets infected with reovirus, and what happens?

A: First, it's important to understand the nature of this type of infection: Infection

is not the same as disease. Infection is just a pathogen going into the body, having an interaction with the body and eventually replicating into the host cells. The result of the infection could vary from clearance, to causing disease, to having chronic infection, which means the virus stays forever in your body. There are different outcomes. So, the term "infection" just means that an

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Essentials Guide
 now available in
 e-book format

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Calendar of
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external pathogen enters the body through a certain route (gastrointestinal, airway, etc.) and replicates into its cells. Whether it causes disease depends on different factors (both viral intrinsic and host intrinsic) that may lead to development of clinical symptoms. So the interaction between a bug and someone's body could result in symptoms, but this is not necessarily the case for all viral infections. Sometimes you don't even know you've been infected because your immune system was able to clear the infec-

tion without any damage or symptoms. The ability to clear the infection also depends on both viral and host factors. Some viruses could be fought efficiently by every human body, while others are set up to chronically live in your cells, most of the times silently without causing any symptom. Reoviruses induce a silent infection; in other words they enter the human body through the oral route and they replicate in the intestine without causing any clinical symptoms, so most affected subjects are not aware that they have been infected.

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Q: How is reovirus in particular related to celiac disease?

A: No evidence supported its role in celiac disease development previously; however, rotavirus, a major cause of gastroenteritis in humans, belongs to the same viral family and was associated with the development of celiac disease by several scientists. Using reovirus, for the first time, we actually proved that a virus, even if it doesn't cause any symptoms, could still act on your immune system in such a significant way that it is able to contribute to elicit an autoimmune disorder. This is not true for all viruses. Indeed in this paper, we used two strains of reovirus, so two slightly different viruses belonging to the same family, and showed that only one of them could have

Q: Who were your subjects?

A: We first tested our hypothesis in common wild-type mice, (we call them wild-type, because they are the strains that exist normally in nature). Then, we used a transgenic mouse model to further correlate what we found with celiac disease onset. The transgenic mouse model we used in the study is engineered to express the human HLA-DQ8 gene, which is one of the two main predisposing alleles for celiac disease development in humans (the other one being HLA-DQ2). All celiac patients must have either one or both of the HLA-DQ2/-DQ8 alleles in order to develop the disease, so this is a requirement. These mice only have the HLA-DQ8, like celiac disease patients, and they are fed with gluten to mimic what happens in the human disease. Of note, the HLA-DQ8 is also expressed by patients with Type 1 diabetes, and this allows for some speculation about the role of similar immunological mechanisms in the context of other autoimmune disorders.

Q: Can you summarize the main conclusions in laymen's terms?

A: In this paper we specifically focus on the loss of immune tolerance to an oral antigen. Oral tolerance is a process normally occurring when we encounter any food protein through an oral route, and it consists of

the development of a tolerogenic response to that protein by our immune system. Sometimes this response is instead inflammatory rather than regulatory, as occurs in celiac disease. Why this shift occurs in some patients to some proteins is unclear. We postulated that viral infections may be one possible trigger of this phenomenon. The first concept this study puts forth is that a viral infection can have an impact on the immune system, independent of the fact that it does not cause symptoms or that it can be efficiently cleared from the body. This specific reovirus strain infects the gut and is efficiently cleared, meaning that we don't detect any more virus a few weeks after infection; nevertheless, for the time that the virus interacts with the immune system, it can impact its response to food antigens, thus promoting a pro-inflammatory rather than a regulatory response to them.

Q: How many of these mice developed celiac disease?

A: These mice do not develop full-blown celiac disease after being infected with reovirus; indeed they don't show any villous atrophy. However, they develop a break of tolerance to gluten, which is a pre-requisite for celiac disease development. In other words, they produce antibodies against gluten and we observe the activation of tissue-transglutaminase in their intestine, a key event occurring in the gut of celiac patients and required for disease development. Transglutaminase deamidates gluten peptides, a process required for gluten to be recognized by the immune system that mounts an inflammatory gluten-specific response. The same transglutaminase is also the one against which celiac-specific auto-antibodies are produced. Both transglutaminase activation and anti-gluten inflammatory response are necessary, but not sufficient, for disease development and do not occur in healthy individuals, but can be already observed in potential celiac patients (subjects with celiac-specific antibodies, but no tissue damage). Our mouse model in the study phenocopies this stage of celiac disease.

Q: What is the evidence that these viruses are associated with celiac disease in humans?

A: We detected higher antibody titers

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against reovirus in patients with celiac disease as compared to controls, thus suggesting that repeated infections by reovirus might be associated to celiac disease development.

In summary, we showed for the first time that reovirus infection is associated with celiac disease. We proved that a clinically asymptomatic virus could have an impact on the intestinal immune system such that it could impair the mechanism of immune tolerance to food proteins, particularly to gluten in a celiac disease-relevant mouse model. This will have an impact not only on the potential development of preventive strategies for at risk subjects (i.e. vaccination against reovirus if developed in the future), but also improve our understanding of how environmental/infectious triggers may contribute to induce autoimmune processes




DR. BANA JABRI, DIRECTOR OF RESEARCH FOR THE CELIAC CENTER, WITH HER RESEARCH TEAM.

[Click here to read the full Science article.](#)

Please click on the link below to learn more about these findings and other work by our team:

www.uchicagomedicine.org/gastrointestinal-articles/seemingly-innocuous-virus-can-trigger-celiac-disease

[Click here for our 2017 Research Report.](#)



DIETITIAN'S CORNER

Lori Welstead, MS, RD, LDN has been on maternity leave. She will be back for the next issue of *Impact*. Until then, we wish Lori and her growing family well! If you have topic ideas you would like to see Lori cover, please send them to cureceliacdisease.org/contact-us/.

Essentials E-Book Now Available!

Our new e-book, Essentials of Celiac Disease and the Gluten-Free Diet, is now available as a free download on Amazon, Barnes & Noble and Apple. The guidebook will help you will learn the basics of celiac disease: signs and symptoms, genetic and antibody testing, diagnosis and required follow-up testing. You will learn what gluten is, where gluten is found and how to avoid it. It will help you make healthy food choices while grocery shopping and preparing foods inside your home to manage your gluten-free diet.

You will be able to identify gluten free grains, meal options and snacks for safe eating anytime. You will learn how to eat gluten free outside your home at social gatherings, restaurants and while traveling. You will also discover the pioneering research initiatives, programs and services offered by the University of Chicago Celiac Disease Center.

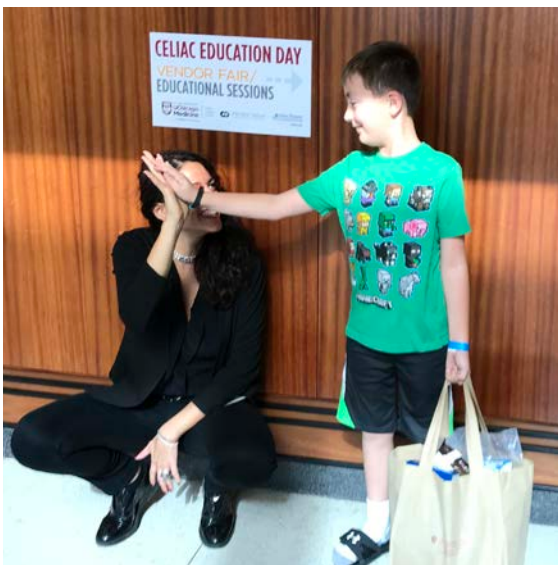
CELIAC EDUCATION DAY 2017

Our 16th annual Celiac Education Day was a truly inspiring event. We welcomed a wonderful crowd for our annual free blood screening and two exceptional presentations. The Q&A panel of experts included Dr. Guandalini and his colleagues, Hilary Jericho, MD, Diane Dewplewski, MD, and dietitian Vicki Gainsburg. The audience seized the rare opportunity to ask these world-renowned experts for answers that many had struggled to find elsewhere. After nearly an hour of this unique interaction, our experts ceded the stage to our Signature Sponsor of the event, The Celiac Disease Foundation (CDF). CDF presented a workshop on becoming a patient advocate. This is an ongoing nationwide initiative of the organization to encourage more funding for celiac disease research. For more information on the patient advocacy training, please visit (www.celiac.org).

During the morning, we tested more than 300 individuals for celiac disease, about 3% of whom were positive for celiac antibodies. Everyone who tested positive received a phone call from Dr. Guandalini or Dr. Semrad, to counsel them on next steps. As in past years, the antibody tests were generously donated by Prometheus Labs, and Peapod generously donated snacks for those getting blood drawn.

Attendees also enjoyed a vendor fair showcasing our partner companies as well as a few special guest organizations including: Barilla, Enjoy Life, Flur Bakery, Full Flavor Foods, Glutino, Kinnikkinnick, King Arthur, Mend Hunger, San-J, Sweet Ali's Gluten Free Bakery, Udi's and Wheat's End.

One unexpected moment was when Preston Stotler, age 8, informed us that he had a donation for the Center. While the money was of course much appreciated, it was how he raised it that really touched our hearts. After he was recently diagnosed, he took it upon himself to take his unused and unopened gluten-containing food from his kitchen to sell to his neighbors. It was these proceeds he wanted to donate to our Center to help fund research for a cure. In a turn of events, Preston's generosity was immediately rewarded: He was one of the two lucky winners of a raffle prize!



Congratulations to Dr. Guandalini!

A Special Message From John M. Cunningham, MD, Chair of Department of Pediatrics and Physician-in-Chief, University of Chicago Medicine Comer Children's Hospital

Please join me in congratulating Dr. Guandalini, who will officially transition to Professor Emeritus during 2018. Dr. Guandalini's career in medicine has spanned over four decades, serving individuals across the globe with celiac disease. In 2001, Dr. Guandalini founded the University of Chicago Celiac Disease Center. Today, thanks to his tireless efforts, our Center is recognized as the most comprehensive celiac center in the world. Through his profound contributions to research and patient care, Dr. Guandalini has made an impact in the world far beyond our Hyde Park campus.

During his time as Medical Director of the Celiac Center, Dr. Guandalini has educated thousands through his eBook, downloaded more than 300,000 times, free screenings, and the Preceptorship training program. He has advocated on the national stage for stricter FDA labeling, and more thorough physician education. The Celiac Disease Center research laboratory was the first to create a mouse model with celiac disease and brought the real promise of a cure into view. Indeed, his dedication to better understanding the disease has kept the Center at the forefront of celiac disease research.

If you would like to show your appreciation for the impact that Dr. Guandalini has made with a donation in his honor, please go to www.cureceliacdisease.org/donate/. We look forward to sharing with Dr. Guandalini the donations made in his name at a "Festschrift" celebration this spring, one of the highest honors bestowed in academia for the most eminent of scholars. We expect this momentous occasion to highlight the impact Dr. Guandalini has had on so many lives.

We appreciate your generosity as we recognize together Dr. Guandalini's remarkable impact on Comer Children's Hospital and celiac research and treatment. With your support, we can continue the programming and research that was rooted in the personalized care he provided to his patients and cement his legacy for the future.



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A Cure for Celiac Disease is possible ...

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PARTNERS:

The University of Chicago Celiac Disease Center is required to raise its own funding, for all research and programming, every year. Our partners are an important part of this effort. We are pleased to partner with the companies listed here, and we thank them for their support.

If your company is interested in partnering with us, please email us at cureceliacdisease.org/contact-us.



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CALENDAR of Upcoming Events:

JANUARY 18, 2017: DR. GUANDALINI speaks about “Gluten-related Disorders in Children” at Grand Rounds at the University of New Mexico Children’s Hospital in Albuquerque, NM.

JANUARY 26 2017: DR. GUANDALINI LECTURES on “Probiotics in Children: What’s the Evidence?” at Grand Rounds in the Department of Pediatrics at the University of Iowa in Iowa City.

FEBRUARY 12, 2018: DR. HILARY JERICHO of The University of Chicago Celiac Disease Center will address the Tri County Celiac Support Group in Farmington Hills, MI, on the topic of The Latest in Celiac Disease Research and Standards.

MARCH 2, 2018: DR. SEMRAD will be addressing the Celiac Disease, Now and in the Future symposium at Columbia University. Her talk is on Diagnosis of Celiac Disease in Adults. For more information, please click [here](#)

APRIL 20, 2018 SPRING FLOURS GLUTEN-FREE GALA: This is a year you won’t want to miss. We will honor Dr. Guandalini for his many years of service to the celiac community and to our Center. Tickets will go on sale in early March. More information will be available soon at cureceliacdisease.org.



EVERY COOKBOOK YOU SEE, CAN NOW BE GLUTEN-FREE

From our new partner, Recipe Revolution:

Designed with YOU in mind, Recipe Revolution converts any recipe to be gluten-free through our dedicated food science.

HOW DOES IT WORK?

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Type in your own dish, or search from thousands of delicious recipe choices.

2. CONVERT IT

Unique food science delivers tailored exchanges of trusted brands for accurate conversions.

3. COOK IT

It’s the same recipe, gluten-free. While keeping taste, texture, and consistency!

