2018 marks an exciting milestone in the history of The University of Chicago Celiac Disease Center: Dr. Guandalini, founder and Medical Director of this world-class Center for more than fifteen years, officially transitions to Professor Emeritus with The University of Chicago Medicine Children's Comer Hospital. Dr. Guandalini has worked day-in and day-out with Dr. Bana Jabri and the many other talented individuals at The Celiac Disease Center for 15 years. Together with his team, he has educated thousands of medical professionals about celiac disease, screened thousands of individuals at risk for celiac disease, oriented thousands of newly diagnosed patients to the gluten-free diet with the Gluten-Free Care Package and now the Essentials Kit and educated hundreds of thousands through our free eBook, recently updated and available on our website. Beyond the education and outreach, the research accomplishments over the last fifteen years have been critical and ground breaking. In fact, these findings have been key in propelling celiac research forward around the globe.

One of the most unique things about The Center is the close collaboration between researchers and clinicians. This collaboration is unparalleled and the secret ingredient to the success in so many of the key discoveries. Dr. Carol Semrad, Dr. Sonia Kupfer and Dr. Hilary Jericho not only care for patients but make a vital contribution to the Center's wealth of knowledge about celiac disease. This unique collaboration between bench research and clinical practice has helped deepen the understanding of celiac disease and its many complex factors.

The successes of The Celiac Disease Center are many, but none of them could have come to fruition without your ongoing financial support. As we enter this new chapter, closer than ever to a cure, we must press on with even greater passion and energy. Dr. Guandalini's transition to Professor Emeritus is a wonderful milestone, and we hope to add another milestone to honor his legacy —the ability to truly fund finding a cure! With your generous support, we can once and for all give Dr. Jabri and her team the funds they need to unravel the mysteries of celiac disease and find a cure. The Center's 2017 Research Report follows with more detail about the progress made over the past year.

If you would like to donate to the important work of The University of Chicago Celiac Disease Center please visit: **cureceliacdisease.org/donate**

RESEARCH AT THE UNIVERSITY OF CHICAGO CELIAC DISEASE CENTER

November, 2017

The core mission of the University of Chicago Celiac Disease Center is to cure celiac disease.

Our Center, founded and led by Dr. Stefano Guandalini, is making great strides in achieving this ambitious goal. The large team led by Dr. Jabri and including her dedicated researchers and both pediatric and adult gastroenterologists have developed a multidisciplinary research program that aims to prevent celiac disease, identify a cure and improve the lives of celiac disease patients and their families. Dr. Jabri is also dedicated to training the next generation of celiac disease researchers and clinicians. The research challenges for celiac disease are similar to those of other autoimmune disorders, and include the complications associated with human research and the difficulty of tackling a complex disorder that involves genetic, environmental, microbial and immune factors.

BELOW IS A SUMMARY OF THE PROGRESS MADE IN THE PAST YEAR AND OF OUR ONGOING STUDIES.

1. WE PUBLISHED A SEMINAL PAPER IN *SCIENCE* THAT DEMONSTRATED THAT VIRAL INFECTIONS TRIGGER DEVELOPMENT OF CELIAC DISEASE. Approximately 30-45% of the U.S. population carries a DQ2 or DQ8 allele, yet less than 1% of the population develops celiac disease. Epidemiological studies suggest that viral infection in early childhood at the time when maternal antibodies are weaning play a role in later development of celiac disease. Thanks to generous donations, we were able to initiate studies that laid the foundation for an NIH grant to study the role of intestinal viruses in celiac disease pathogenesis in collaboration with Drs. Terrence Dermody (University of Pittsburgh) and Ramnik Xavier (Massachusetts General Hospital and Broad Institute). Our study shows unambiguously that reovirus infections at the time of gluten introduction in children confuses the immune system and triggers the development of an aggressive inflammatory immune response against gluten as if it were itself a virus. This publication has received impressive international coverage with mainstream press such as the *Wall Street Journal* reporting on the study. WE NOW ARE WORKING ON DEFINING VACCINE STRATEGIES AND EXPANDING THE STUDIES TO ANOTHER VIRUS, NOROVIRUS, WHICH WIDELY INFECTS CHILDREN TO DETERMINE WHETHER IT CAN ALSO TRIGGER DISEASE. We are also working on identifying pathways common to all viruses that induce loss of tolerance to gluten, with the idea of targeting these pathways to treat and prevent celiac disease.

2. OUR MONTELUKAST CLINICAL TRIAL, AN FDA-APPROVED DRUG FOR ASTHMA THAT BLOCKS CYSTEINYL LEUKOTRIENES, SUGGESTS THAT MONTELUKAST HAS ANTI-INFLAMMATORY PROPERTIES IN CELIAC DISEASE PATIENTS UNDERGOING A GLUTEN CHALLENGE. The clinical trial was initiated by Dr. Sonia Kupfer at the University of Chicago, because research in Dr. Jabri's laboratory—published in the *Journal of Experimental Medicine*--revealed a role for cysteinyl leukotrienes in the pathogenesis of celiac disease. VERY ENCOURAGING DATA IN A PRELIMINARY CLINICAL TRIAL COMPRISED OF TEN PATIENTS INDICATE THAT MONTELUKAST MAY BE ABLE TO ALLEVIATE INFLAMMATION IN CELIAC DISEASE PATIENTS EXPOSED TO GLUTEN. The data suggest that Montelukast may have a beneficial effect in the context of accidental gluten ingestion, may accelerate healing in patients starting a gluten-free diet, and may promote healing in patients in whom exclusion of gluten failed to fully heal the intestine. We are now looking for funding to expand the clinical trial to investigate further whether Montelukast could be used as an adjunct therapy to a gluten-free diet.

3. COMPLETION OF A CLINICAL TRIAL IN CELIAC DISEASE PATIENTS WHO DO NOT RESPOND TO A GLUTEN-FREE DIET.

There is currently no effective treatment for refractory celiac disease, a rare, but severe precancerous complication of celiac disease. We are currently analyzing the results of a clinical trial testing the efficacy of a drug blocking the IL-15 signaling pathway in patients with refractory celiac disease. WE SHOWED THAT IL-15, A STRESS-INDUCED CYTOKINE, IS OVEREXPRESSED IN THE GUT OF CELIAC DISEASE PATIENTS AND PLAYS A CRITICAL ROLE IN THE DESTRUCTION OF THEIR INTESTINAL LINING. This trial is sponsored by the NIH and conducted in collaboration with Professor Thomas Waldmann (NIH/NCI) and Professor Joseph Murray (Mayo Clinic). In parallel, the company Celimmune has finalized a phase 2 trial blocking IL-15 in refractory celiac disease. These clinical trials show how discoveries made at the bench can translate into treatment for patients.

4. STUDIES DETERMINING THE ROLE OF THE MICROBIOTA IN CELIAC DISEASE. The human body harbors more than 40 trillion microbial cells. These microbes are critical for our health: they provide nutrients and metabolites, contribute to the health of our tissues and help tune our immune system. However, under certain circumstances, deleterious microbes outgrow good microbes and prevent them from exerting their beneficial effects. Last year we published in the *ISME Journal*, a highly regarded multidisciplinary journal of microbial ecology, that IL-15 overexpression is associated with shutting down production of butyrate by the microbiota. Butyrate is a critical health-promoting short chain fatty acid. WE ARE CURRENTLY STUDYING HOW TO RESTORE BUTYRATE PRODUCTION AND A NORMAL MICROBIOTA IN THE STERILE INFLAMMATORY ENVIRONMENT OF THE GUT OF CELIAC DISEASE PATIENTS.

5. GENERATING RELEVANT MOUSE MODELS FOR CELIAC DISEASE. The lack of a relevant mouse model of celiac disease has been a major limitation in the field of celiac disease. Such preclinical models are essential to test new therapeutic avenues. We are finalizing a manuscript reporting the development of the first relevant mouse model of celiac disease. We are currently using this preclinical mouse model to test several therapies. WE HAVE PRELIMINARY DATA SUGGESTING THAT INHIBITORS OF TISSUE TRANSGLUTAMINASE-2 DEVELOPED BY OUR COLLABORATOR DR. CHAITAN KHOSLA (an internationally renowned chemist at Stanford University) can prevent celiac disease. We are expanding these studies and planning on reporting them in a manuscript next year. It is of note that at the International Celiac Disease Symposium last September, the report on the mouse model received an award for the most meaningful new discovery reported at the meeting.

6. ADDRESSING THE COMPLEXITY AND HETEROGENEITY OF CELIAC DISEASE.

(i) Celiac disease can develop in children shortly after gluten introduction, but it can also develop later in life, including in the elderly. Is celiac disease the same disease in children and adults? (ii) Celiac disease occurs more frequently in women than men. Why, and is it the same disease? (iii) Some patients, called potential celiac disease patients, lose tolerance to gluten, have anti-gluten and anti-tissue transglutaminase antibodies, and yet their intestinal lining is intact. Why is the intestine of these patients protected? (iv) Conversely, some family members show signs a stressed intestinal lining and yet they remain tolerant to gluten. Why? (v) Is the gut of celiac disease patients on a gluten-free diet completely normal? Do children heal better than adults with celiac disease? (vi) Finally, why do certain celiac disease patients respond poorly to a gluten-free diet and even become refractory? To address these questions, WE WILL BE USING GENOMICS AND WILL ENGAGE IN A MASSIVE SEQUENCING EFFORT TO ANALYZE MORE THAN 300 TRANSCRIPTOMES OF THE GUT FROM CONTROL INDIVIDUALS WITH A NORMAL GUT, ADULTS AND CHILDREN WITH ACTIVE CELIAC DISEASE, PATIENTS WITH POTENTIAL CELIAC DISEASE, AND PATIENTS ON A GLUTEN-FREE DIET RESPONDING WELL AND POORLY TO IT. This study will provide unique insights into the heterogeneity and triggers of celiac disease, and will help decipher the mechanisms underlying a poor response to the gluten-free diet. It will provide a foundation for precision medicine that will enable us to develop targeted and effective prevention and treatment for each individual and family with celiac disease.

We cannot begin to express our gratitude to our donors and our celiac disease patients and their families for their trust and ongoing support. Thanks to them, the University of Chicago Celiac Disease Center is today a world-renowned center for celiac disease, known for its transformative research in celiac disease. The scarce NIH funding and the lack of a national organization funding pioneering, high-risk/high-impact celiac disease research is a significant impediment for innovation and discoveries. With your help, Dr. Jabri, her team and the physicians of the Celiac Disease Center at the University of Chicago will continue to expand a multidisciplinary research program that engages researchers and clinicians from all over the world to tackle celiac disease and develop a cure for all patients. These are exciting times and we look forward working with you.

For more information, please visit

cureceliacdisease.org

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