THE UNIVERSITY OF CHICAGO MEDICINE

Celiac Disease Center

cureceliacdisease.org

The University of Chicago Celiac Disease Center's vision is defined by its goal to prevent and cure celiac disease. To tackle celiac disease, Dr. Jabri has developed a multifaceted and multidisciplinary approach in close collaboration with her clinical colleagues Drs. Guandalini, Semrad and Kupfer, and prominent research groups across the world and across disciplines.

This report gives a summary of the progress made in the past year and of ongoing studies.

RESEARCH AT THE UNIVERSITY OF CHICAGO CELIAC DISEASE CENTER

November, 2015

THE YEAR'S MAJOR ACHIEVEMENTS:

1. Publication in the highest impact specialty journal, *Gastroenterology*, that reports the finding that a subset of family members of those with celiac disease have anomalies in their intestinal lining (epithelial cells). While classical analysis of their biopsies reveals no morphological anomalies of the intestine, state of the art technologies reveal the presence of important alterations. This important finding provides an explanation as to why these individuals have symptoms even though they do not display any of the classical features of celiac disease. It sets the stage for studies aimed at identifying diagnostic markers for individuals who suffer from gluten ingestion but are not celiac. It is important to point out that the so-called "gluten sensitivity" is an "umbrella" term comprising several, yet poorly defined, conditions. This fundamental discovery was highlighted in a News & Views in the prominent journal *Nature Reviews, Gastroenterology & Hepatology.*

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2. Publication in the high impact *Journal of Experimental Medicine,* with News & Views, that reveals that the lipid signaling molecules cysteinly leukotrienes are highly increased in patients with celiac disease and are involved in tissue destruction. Interestingly, the same pathway is dysregulated in patients with asthma. Dr. Sonia Kupfer, adult gastroenterologist at University of Chicago, has obtained funding to launch a clinical trial to test Montelukast, an FDA approved drug for asthma, that blocks cysteinly leukotrienes in adult celiac disease patients.

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3. We obtained National Insititutes of Health (NIH) funding (R01) to conduct studies aimed at characterizing how acquired genetic (epigenetic) changes may play a role in celiac disease, and determining whether molecules that reverse these epigenetic alterations can be used to treat celiac disease, in particular in those patients who respond poorly to the gluten free diet.

This important finding ... sets the stage for studies aimed at identifying diagnostic markers for individuals who suffer from gluten ingestion but are not celiac.

ONGOING STUDIES:

1. WE ARE DETERMINING THE ROLE OF VIRAL INFECTIONS IN CELIAC DISEASE. The prevalence of celiac disease continues to rise, suggesting that environmental factors must trigger and precipitate disease. For a long time it was suspected that viruses may play a role in celiac disease, and more generally in autoimmunity. Thanks to generous donations, we were able to initiate studies and gather preliminary data that have allowed us to obtain NIH funding to study the role of intestinal viruses in celiac disease pathogenesis. These studies will determine whether viruses can induce loss of oral tolerance to gluten. If confirmed, it will support development of vaccines, in particular for children who have a high risk for celiac disease.

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2. WE CONTINUE TO BE AT THE FOREFRONT OF DEVELOPING RELEVANT MOUSE MODELS FOR CELIAC DISEASE. These models allow us to establish cause-effect relationships, and to validate new therapeutic avenues. We are currently testing promising inhibitors of tissue transglutaminase-2, in a preclinical mouse model of celiac disease generated in our laboratory. These pharmacological inhibitors were developed by our collaborator, Dr. Chaitan Khosla, an internationally renowned chemist at Stanford University who has made important contributions to the field of celiac disease. These studies will provide the scientific basis to move inhibitors of tissue transglutaminase-2 to clinical trials.

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3. WE HAVE ACQUIRED THE TECHNOLOGY TO SET-UP MINI-GUT MODELS FROM INDIVIDUALS WITH CELIAC DISEASE. These "test tube mini-guts" retain the genetic characteristics of the individual from whom they came. This is part of our general effort to understand the heterogeneity of celiac disease and move towards developing personalized medicine for patients with celiac disease.

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4. CLINICAL TRIAL IN CELIAC DISEASE PATIENTS THAT ARE REFRACTORY TO GLUTEN-FREE DIET. There is currently no effective treatment for refractory celiac disease. Based on encouraging results, we are continuing to enroll patients with refractory celiac disease in a clinical trial testing the efficacy of a drug blocking the cytokine IL-15, which we have identified as playing a critical role in celiac disease. This trial is sponsored by NIH and conducted in collaboration with Professor Waldmann (NIH/NCI) and Professor Murray (Mayo Clinic).

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5. ASSESSMENT OF THE EFFICACY OF THE GLUTEN-FREE DIET (GFD) IN RESOLVING THE EXTRA-INTESTINAL MANIFESTATIONS OF CELIAC DISEASE. While it is well known that celiac patients with gastrointestinal issues typically respond soon to the GFD, there is little information on how effective the diet can be on symptoms such as headaches, short stature, anemia, and other non-gastrointestinal problems. Our investigation on almost 500 patients has shown in preliminary data that most symptoms improve with time, but children respond more promptly and completely than adults.

We thank our celiac disease patients and their families for their enthusiasm, their trust and their ongoing support. Their commitment has played a major role in putting the University of Chicago Celiac Disease Center at the forefront of research in celiac disease. Thanks to their help, we are continuing to make transformative discoveries and move celiac disease research to new frontiers. Our scientific team continues to work tirelessly with the University of Chicago clinical pediatric and adult gastroenterology team, world-renowned in clinical care of celiac disease, to identify a cure and improve the life of celiac disease patients and their families.