ImmusanT Inc.
One Kendall Square
Suite B2004
Cambridge, MA 02139
Office 617-299-8399
Fax 617-300-8892
Email info@ImmusanT.com

Transforming celiac disease from a digestive disease to an immune disease: and restoring tolerance to gluten in celiac disease

Bob Anderson MBChB PhD FRACP, Chief Scientific Officer, ImmusanT, Inc. Cambridge USA.

Scientific breakthroughs can turn out to be a flash in the pan, while the impact of others may only be apparent many years later. The science behind ImmusanT's current clinical trials of Nexvax2, the "celiac vaccine", underway in New Zealand, Australia, and the USA has evolved over more than 20 years. Looking back at the scientific breakthroughs in celiac disease over the last sixty years, it is clear that the critical turning point that has (eventually) led to Nexvax2 being tested in patients was discovery that "the gene" determining susceptibility to celiac disease, HLA DQ, is an immune response gene and not a gene for a digestive enzyme or one that might cause leakiness in the gut. This discovery began a deep conceptual shift in understanding celiac disease.

Celiac disease cannot be cured by removing a section of bowel, nor is it cured by removing gluten from the diet. The problem in celiac disease lies in the immune system. Thinking of celiac disease as a disease of the immune system rather than the diet or digestive system has profound implications for the future management of celiac disease.

Gluten is just one of millions of antigens the immune system recognizes and "decides" whether to threat as a friend or foe. In celiac disease, gluten comes to be treated as a threat and stimulates an aggressive, inflammatory reaction as the immune response tries to "eradicate" gluten from tissues, primarily the lining of the gut. The human immune system is complex – it is flexible and is educated by signals from the environment before "deciding" how to respond to antigens like gluten or components of viruses and bacteria. "Decisions" made by the immune system are "remembered", but are always under review and in special circumstances can be modified or even reversed.

Once celiac disease is established, eating gluten stimulates a very small, specific set of "memory T cells" that focus exclusively on components of gluten. Usually there are so few gluten-reactive T cells in blood they cannot be measured, but when the gluten immune response is reactivated in someone with celiac disease by 3-day "gluten challenge", gluten-reactive T cells can be measured in blood six days later. Studies measuring and characterizing these gluten-reactive T cells in blood over the last 12 years has led to the design of Nexvax2. Nexvax2 is a "gluten-specific therapeutic vaccine" designed for patients that carry HLA DQ2.5. It is a mixture of three synthetic peptides based on gluten fragments commonly recognized by T cells that would

normally sense gluten absorbed from the gut. Nexvax2 is being tested in volunteers carrying the genes for HLA DQ2.5 and have had celiac disease diagnosed by biopsy who now follow a strict gluten free diet. The current clinical trials are to test the safety and tolerability of repeated doses of Nexvax2 in adults with HLA DQ2.5+ celiac disease. Later studies will test whether Nexvax2 can restore immune tolerance to gluten and allow a normal diet in patients with celiac disease.

As the first treatment intended to replace gluten-free diet in the treatment of celiac disease, development of Nexvax2 has stimulated interest around the world. Celiac disease is also gaining a lot of attention in the pharmaceutical world because it appears to be one of the best candidates for a treatment that could reverse a decision by the immune system to react aggressively to an antigen (gluten). However, in the "big picture" celiac disease is not unique, there are a variety of experimental "antigen-specific therapies" for cancers, transplant rejection, drug reactions, and allergies, that each aims to reverse decisions by the immune system to "tolerate" or "eradicate" cancers, transplants, allergens or self-antigens causing autoimmune disease.

Looking back at developments in celiac disease, the first "revolution" was triggered by Dicke's discovery in 1950 that dietary gluten caused relapse and Paulley's report in 1954 that showed intestinal damage. Celiac disease became treatable with gluten free diet, and diagnosed by biopsy of the small intestine. Doctors who perform biopsies of the intestine, dietitians who educate patients about gluten free diet, and the food industry supplying gluten free food will continue to play critical roles in diagnosis and management of patients affected by celiac disease, but there was a second revolution in celiac disease that began in 1989. Today millions of people around the world have already benefited from the "immunological revolution" in celiac disease. The initial blood test for celiac disease performed in millions of people every year detects antibodies to gluten peptides and transglutaminase that are triggered by the immune response to gluten. The HLA DQ genetic test is increasingly used to identify people who unnecessarily avoid gluten in their diet, who have been mistakenly diagnosed with celiac disease, or who are at increased risk and may need to be monitored for development of celiac disease. We are now entering a new phase in the history of celiac disease with development of diagnostic tests and treatments that seek to overcome the need for gluten free diet by restoring immune tolerance to gluten.

Key events in understanding and managing celiac disease leading to testing of Nexvax2 (Quotes and dates refer to publications in medical and scientific journals, or press releases)

Drs Dicke, Weijers and van de Kamer; Utrecht, Netherlands; January 1950:
"Attention is drawn to the different effects of different kinds of cereals and starches on patients with celiac disease. The effect of wheat flour is unfavourable while that of wheat starch is harmless. The harmful effect is produced by a still unknown substance and not by starch. The substance in question is provisionally called the "wheat factor." The effect of this factor is judged according to its ability to produce or aggravate anorexia, vomiting, diarrhoea and steatorrhoea. Several conclusions as to the significance of this factor are presented.

Drs van de Kamer, Weijers and Dicke; Utrecht, Netherlands; May 1953:

“Based on the results of an investigation of a number of patients with celiac disease, the harmful action of wheat flour was shown to be chiefly inherent to the gliadin fraction.”

Dr Paulley; Ipswich, England; December 1954:
“Three cases of idiopathic steatorrhoea [fatty stools believed to be caused by celiac disease] and a doubtful fourth case are described in which biopsy material was taken at laparotomy. All showed chronic inflammation of the jejunum and lymph nodes.”

Dr C. Anderson; Melbourne, Australia; October 1960:
“The present study demonstrates the histological changes in the duodenal mucosa in biopsy material from a group of newly diagnosed young celiac patients and the complete or partial disappearance of these changes during the first year of treatment in patients of this group from whom subsequent biopsies have already been obtained.”

Drs C. Anderson, Gracey and Burke; Birmingham, England and Perth, Australia; April 1972:
“The two major theories are the 'toxic' and the 'immunological'. … It could be via a cellular-mediated immune mechanism, but further studies are certainly needed, particularly in young newly diagnosed cases, before these controversial theories can be finally settled.”

Drs Baker and Read; Bristol, England; May 1976:
“It is therefore suggested that oats and barley in addition to wheat and rye be excluded from the diet of celiac patients and that this regime should be enforced with particular rigour in patients who have not satisfactorily benefited from prolonged gluten withdrawal.

Drs Anand, Piris, and Truelove; Oxford, England; January 1978:
“The biopsy specimens obtained before and after challenge (eating cereals) were compared in terms of histology …. results indicate that rye and barley are harmful but that maize and rice are harmless.”

Dr Kasarda and collegues; Berkeley, California; April 1984:
“We report here the primary sequences of α-type gliadins determined by DNA sequencing of complementary DNA (cDNA) clones and by amino acid sequencing of A-gliadin (an aggregable type of α-gliadin).”

Drs Sollid and Thorsby; Oslo, Norway; January 1989
“Here we report that all except one of these CD patients carry DQAI and DQB1 genes that may encode the same DQ a/ß heterodimer”

Dr Lundin and colleagues; Oslo, Norway; July 1993:
“The findings suggest preferential mucosal presentation of gluten-derived peptides by HLA-DQ(α1*05,βI*0201) in CD, which may explain the HLA association. ”

Dr Dieterich and colleagues; Berlin, Germany; July 1997:
We identified tissue transglutaminase as the unknown endomysial autoantigen.

Dr Dieterich and colleagues; Berlin, Germany; December 1998:
An ELISA based on tTG allows diagnosis of celiac disease with a high sensitivity and specificity. …. Because the assay is quantitative, not subjected to interobserver variation, and easy to perform, it will be a useful tool for population screening of a hitherto underdiagnosed disease."

Dr R Anderson and colleagues; Oxford, England; March 2000:
"Our studies here have identified an immunodominant CD- specific epitope and an immune response induced by bread challenge, thereby providing a defined target for immuno-modulation. These findings indicate several possible alternatives for the treatment of celiac disease."

Dr Arentz-Hansen and colleagues; Oslo, Norway; March 2000:
"Here we have demonstrated that intestinal T cell recognition of an immunodominant fragment of α-gliadin is dependent on the enzymatic modification of a single glutamine residue. These findings provide a new molecular perspective to analyze the mechanisms leading to wheat intolerance in CD that should yield new insights into the mechanisms of oral tolerance in humans.

Dr Tye-Din and colleagues; Melbourne, Australia; July 2010:
"Our study now allows the design of a potential immunotherapy with peptides confirmed as immunodominant in a common human immune disease. The lead compound consists of three immunogenic gluten peptides, which are now in phase I clinical development. A critical step toward a peptide-based immunotherapy for CD will be to show that such a compound is bioactive and targets relevant T cells when administered to volunteers with HLA-DQ2–associated CD. Provided these fundamental immunological properties and safety are established, such a compound promises to provide unique insights into the therapeutic potential of peptides confirmed to be disease-specific T cell agonists."

ImmusanT, Inc.; Cambridge Massachusetts USA; May 2011:
ImmusanT, Inc., a biotechnology company developing an immunotherapeutic vaccine, companion diagnostic and monitoring tool for celiac disease, reported results from a Phase 1 study evaluating the safety, tolerability and bioactivity of Nexvax2® in patients with celiac disease.

ImmusanT, Inc.; Cambridge Massachusetts USA; September 2012
ImmusanT announced today that it has initiated clinical trials in New Zealand, Australia and the U.S. to further evaluate the safety and tolerability of Nexvax2®, the first therapeutic vaccine for patients with celiac disease. Nexvax2 is designed to re-establish patients' tolerance to the toxic effects of gluten, a protein in wheat, barley and rye, and allow them to return to a normal diet. There are currently no approved medicines available for people with celiac disease, who must manage their condition by eliminating gluten-containing foods from their diet."