Intercepting IL-15 in celiac disease

By Tim Fulmer, Senior Writer

A group of American and Japanese researchers has shown that blocking IL-15 signaling decreased inflammation and tissue damage associated with celiac disease in mice.¹ They now hope to acquire funding to test the strategy in the clinic, where it could help patients who fail to respond adequately to nutritional therapy.

Each team had separately zeroed in on IL-15 as a key player in lymphoid malignancies and autoimmune diseases. **National Cancer Institute** researchers are running a Phase I trial of an IL-15 receptor-targeting antibody to treat T cell lymphocytic leukemia,² whereas the Japanese researchers are studying IL-15's role in gastrointestinal autoimmune disease.³

The two groups have now joined forces to test the IL-15 receptor-targeting antibody in mice that show gut inflammation similar to that seen in patients with celiac disease.

Figure 1. The pathogenesis of celiac disease. The disease starts with the ingestion of gluten, which is present in wheat, barley and rye products. Enzymes in the lumen of the small intestine break down gluten into immunogenic peptides [a] that cross the intestinal epithelium and enter the lamina propria, a connective layer that contains capillaries and lymphoid tissue and provides support to the intestinal mucosa [b].

Within the lamina propria, the gluten-derived peptides encounter the host immune system and are taken up and presented by anti-gen-presenting cells (APCs) to CD4⁺ T cells [c].

CD4⁺ cells activated by the peptides secrete multiple proinflammatory cytokines, including IL-15 [d], and trigger B cells to produce antibodies against the peptides [e]. The resulting inflammation damages the intestinal mucosa and leads to nutrient malabsorption, diarrhea, fatigue and weight loss.

Standard of care for celiac disease is a gluten-free diet. In the *Proceedings of the National Academy of Sciences* paper, the authors show that an antibody designed to block IL-15 can reduce mucosal damage. The National Cancer Institute is conducting a Phase I trial of a mAb against CD122 (IL-2 receptor β -chain), a subunit of the IL-15 receptor, for leukemia.

The two therapies in clinical development to treat the disease as adjuncts to a gluten-restricted diet act upstream from IL-15. Also, **Nexpep Pty. Ltd.** is developing Nexvax2, a vaccine in Phase I testing that is comprised of commonly recognized gluten peptides.

Celiac disease is unique among autoimmune disorders because its triggering antigen has been identified—dietary gluten. Standard care is thus strict avoidance of gluten-containing foods, and the two most advanced therapies in the clinic target gluten in the intestinal lumen before it can interact with the body's immune system to trigger production of proinflammatory cytokines and chemokines (see **Figure 1, “The pathogenesis of celiac disease”**).^{4,5}

The latest findings, published in the *Proceedings of the National Academy of Sciences*, build on previous work by the Japanese researchers that showed that overexpression of human IL-15 in the mouse intestinal epithelium led to significant inflammation in regions of the small intestine closest to the stomach.³ Those inflammatory lesions showed some of the hallmarks of celiac disease, including significant atrophy of the intestinal villi and infiltration of proinflammatory CD8⁺ cells.

Based on that finding, the researchers hypothesized that inhibiting IL-15 signaling in the same mice could help reduce inflammation and offer a new strategy for treating celiac disease. Indeed, mice given an antibody against CD122 (IL-2 receptor β -chain), one of the three subunits of IL-15's receptor, had significantly fewer inflammation-associated histological abnormalities in the small intestine than untreated controls.

One potential drawback of targeting IL-15, according to Bana Jabri, associate professor of medicine and pathology and researcher in the Celiac Disease Center at **The University of Chicago**, is that blocking the cytokine has “the potential for dangerous immunosuppressive side effects. IL-15 has potent immune effects and may play an important role

in protecting against infection.”

Indeed, the proliferation and effector functions of antiviral CD8⁺ T cells are known to be generally sensitive to IL-15 levels.^{6,7}

According to the authors of the *PNAS* article, the antibody “would not likely result in the profound immunosuppression that would occur with total elimination of CD8⁺ T cells.” The reason, they wrote in the paper, is that the antibody only reduced levels of a subset of pathogenic proinflammatory CD8⁺ cells from the intestinal mucosa and did not affect other CD8⁺ subpopulations that are essential to the host antiviral response.

Nevertheless, Daniel Adelman, SVP and CMO of **Alvine Pharmaceuticals Inc.**, said the potential for serious immunosuppressive side effects warrants studying the approach in a variety of preclinical disease models. “Those studies should allow us to better understand the potential scope of off-target toxicity associated with chronic blockade of IL-15 signaling in autoimmune and inflammatory disease,” he said.

Alvine is developing ALV003, a combination of a glutamine-specific cysteine protease (EP-B2) and a proline-specific prolyl endopeptidase (PEP) engineered to degrade gluten into nonimmunogenic fragments in the stomach. It is in Phase II testing to treat celiac disease in combination with a gluten-restricted diet.

Three principal investigators participated in the *PNAS* study: Thomas Waldmann, chief of the National Cancer Institute’s metabolism branch; Liyanage Perera, a staff scientist in the metabolism branch; and Takachika Hiroi, a researcher in the Department of Allergy and Immunology at **The Tokyo Metropolitan Institute of Medical Science**.

Finding the right patients

Corresponding author Waldmann told *SciBX* the IL-15 receptor–targeting antibody’s niche in the celiac space will be in the 10% of patients with refractory disease. In those patients, who do not respond to gluten-free diets, proliferation of CD8⁺ cells in the small intestine can ultimately lead to CD8⁺ T cell lymphoma.

Francisco Leon, VP and CMO of **Alba Therapeutics Corp.**, told *SciBX* that a potential advantage of targeting IL-15 in refractory disease could be the higher selectivity and improved safety over broad-spectrum anti-inflammatory drugs and steroids. Those drugs can reduce aberrant T cell proliferation but carry a higher risk of infection and malignancy.

Alba’s larazotide acetate (AT-1001), a synthetic peptide that targets the tight junction protein to block intestinal permeability to gluten, is in Phase IIb testing to treat celiac disease in combination with a gluten-restricted diet. **Shire plc** has exclusive rights to commercialize larazotide outside the U.S. and Japan.

Waldman said a humanized version of the anti-CD122 antibody has shown safety in the ongoing Phase I leukemia trial. In the near future,

he said, he wants to start a Phase I trial of the antibody to treat refractory celiac disease. He is looking for funding from company or university sources and hopes to form a multi-institution collaboration to organize and run the trial.

Blocking IL-15 has been tried in other autoimmune indications. **Celonic AG**’s CRB-15, a point-mutated recombinant IL-15 fusion protein that binds the IL-15 receptor and inhibits signaling, is in preclinical development for rheumatoid arthritis (RA), psoriasis and Crohn’s disease. According to CEO and Managing Director Andreas Herrmann, the compound has shown efficacy and safety in a number of preclinical autoimmune models.⁸

In 2008, **Amgen Inc.** and **Genmab A/S** discontinued development of AMG 714 after the mAb targeting IL-15 did not show efficacy in Phase I and Phase II trials to treat psoriasis and RA, respectively, according to Amgen spokesperson Sonia Fiorenza. The compound was safe, she added.

Waldmann and the U.S. government have a U.S. patent covering the use of CD122-targeting antibodies to treat autoimmune disease and malignancies. The patent is available for licensing.

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COMPANIES AND INSTITUTIONS MENTIONED

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Alvine Pharmaceuticals Inc., San Carlos, Calif.
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Celonic AG, Juelich, Germany
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Nexpep Pty. Ltd., Ivanhoe, Victoria, Australia
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