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Investigational therapies for celiac disease and refractory celiac disease

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Celiac disease is managed with a life-long strict adherence to a gluten-free diet, since there are no medications approved to treat this common diet-induced autoimmune disease.[1] Unfortunately, strict compliance with a gluten-free diet is very difficult in practice due to the widespread presence of gluten in foods. For this reason, more than 50% of celiac subjects following a gluten-free diet continue to suffer from clinically relevant disease activity (intestinal mucosal atrophy, symptoms and/or autoantibodies),[2,3] what is called Non-Responsive Celiac Disease.[4] In addition, a small fraction (~0.5%) of celiac patients develop a potentially fatal complication of celiac disease, the development of an intestinal lymphoma termed Refractory Celiac Disease Type II (RCD-II).[5] Novel experimental therapies are being studied to increase the management options for NRCD and RCD-II patients, aided by new assays to measure and monitor gluten in the diet.[6]

In order of most-to-least advanced products in the pipeline, the following experimental medications are in active clinical development:

- Larazotide acetate (INN-002, formerly AT-1001), a tight-junction modulator, has completed phase 2b and reduces the para-cellular passage of gluten to the *lamina propria*.[7]
- The endopeptidase latglutenase (IMGX-003, formerly ALV003) has completed phase 2b and breaks down gluten to produce less or non-toxic peptide fragments.[8]
- The anti-IL-15 monoclonal antibody AMG 714, which blocks IL-15, a key mediator of the pathophysiology of celiac and refractory celiac disease[9-11] is currently in phase 2a studies in NRCD and RCD-II.
- The anti-IL-15-Receptor monoclonal antibody HuMik1b is currently in phase 2a for RCD-II.
- The leukotriene receptor antagonist montelukast is currently undergoing a Ph2a gluten challenge study.
- The therapeutic vaccine, NexVax2, is being tested in phase 1b studies in celiac patients with the aim of inducing gluten tolerance via regulatory T-cells.[12]
- The gluten-binding polymer BL-7010, which sequesters gluten in the intestinal lumen to reduce exposure to the immune system,[13,14] has completed phase 1b testing.
- The anti-gliadin avian immunoglobulin IgY[15] is in phase 1/2 in celiac patients.
- The transglutaminase inhibitor ZED1227, which blocks a key enzyme in the pathophysiology of celiac disease,[16] has completed phase 1 testing.
- The cathepsin S inhibitor RG7625 is undergoing Ph1b testing in celiac patients.

The full list of clinical and pre-clinical programs at the date of this writing and the parent organization sponsoring the studies is presented in Figure 1 (adapted from Schuppan et al, 2009[17]).

While substantial progress has been made in the last few years in the development of experimental medications for celiac disease, these therapies remain in early- or mid-phases of clinical research, and additional effort is required to provide alternative management options to patients with celiac disease.

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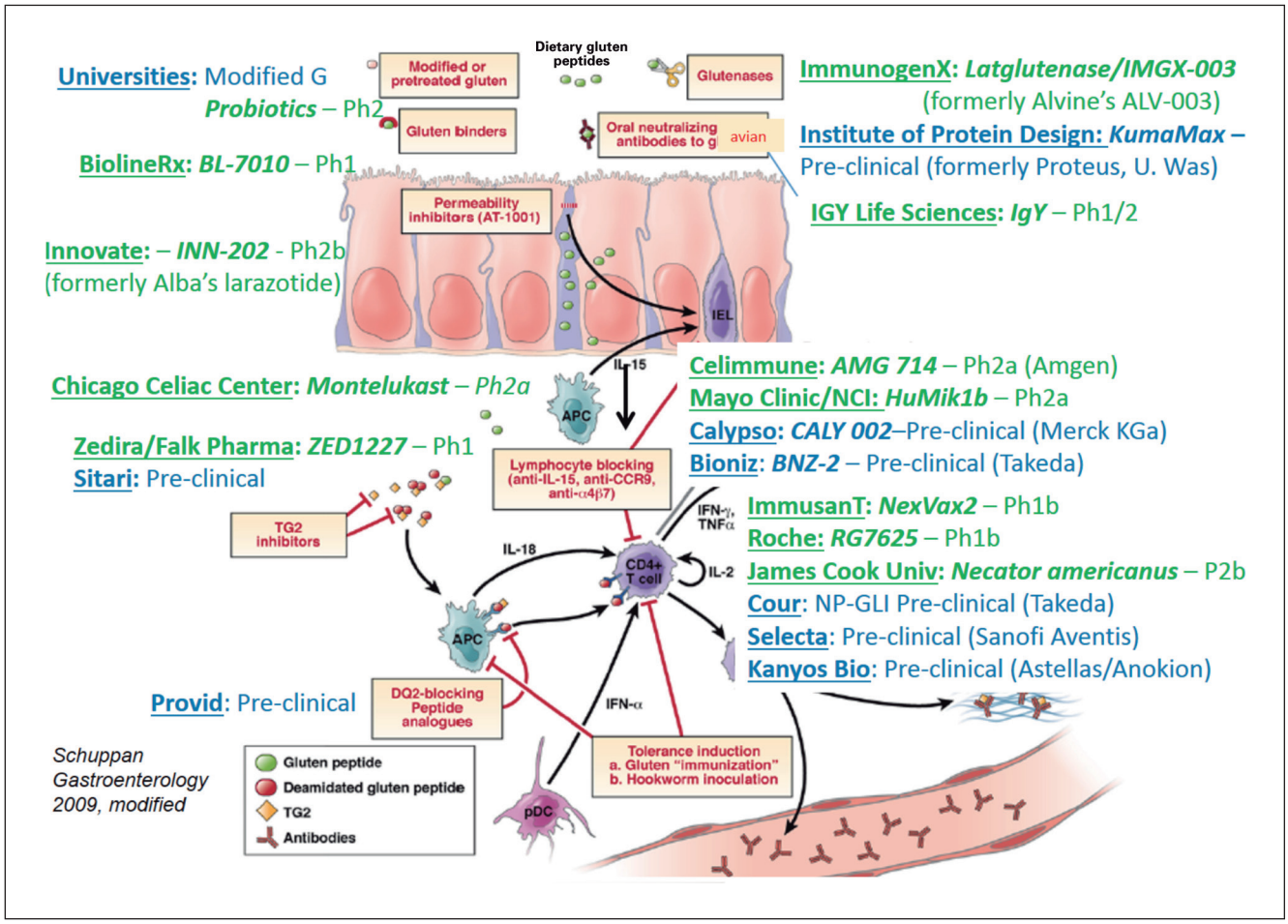

Figure 1

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