Are we close to a pharmacological therapy for Celiac Disease?

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Medical Director, Celiac Center, BIDMC
Professor of Medicine
Co-founder, Celiac Program
Harvard Medical School
<table>
<thead>
<tr>
<th>Commercial or Non-Profit Interest</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvard Medical Faculty Physicians</td>
<td>Faculty member, employee</td>
</tr>
<tr>
<td>Celiac Center at BIDMC, Boston</td>
<td>Co-founder &amp; Medical Director</td>
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<tr>
<td>Harvard Medical School - Celiac Research Program</td>
<td>Co-founder</td>
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<tr>
<td>North American Society for the Study of Celiac Disease</td>
<td>Committee member, President-elect</td>
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<tr>
<td>Foundation for Celiac Disease Outcomes Measures (FCDOM)</td>
<td>Co-founder, Secretary</td>
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<td>Current Opinion in Gastroenterology</td>
<td>Editor in Chief</td>
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<tr>
<td>Celimmune</td>
<td>Scientific advisory board member</td>
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<td>Cour Pharma</td>
<td>Scientific advisory board member,</td>
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<td></td>
<td>Stockholder</td>
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<td>Glutenostics</td>
<td>Scientific advisory board member,</td>
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<td>Innovate</td>
<td>Scientific advisory board member</td>
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<td>ImmunogenX</td>
<td>Scientific advisory board member</td>
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<td>Takeda Pharmaceuticals</td>
<td>Scientific advisory board member</td>
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<td>Role</td>
<td>Description</td>
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<tr>
<td><strong>Medical Expert</strong></td>
<td>(as <em>Medical Experts</em>, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. <em>Medical Expert</em> is the central physician Role in the CanMEDS Framework and defines the physician’s clinical scope of practice.)</td>
</tr>
<tr>
<td><strong>Communicator</strong></td>
<td>(as Communicators, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)</td>
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<tr>
<td><strong>Collaborator</strong></td>
<td>(as <em>Collaborators</em>, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)</td>
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<tr>
<td><strong>Leader</strong></td>
<td>(as <em>Leaders</em>, physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.)</td>
</tr>
<tr>
<td><strong>Health Advocate</strong></td>
<td>(as <em>Health Advocates</em>, physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.)</td>
</tr>
<tr>
<td><strong>Scholar</strong></td>
<td>(as <em>Scholars</em>, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)</td>
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<tr>
<td><strong>Professional</strong></td>
<td>(as <em>Professionals</em>, physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.)</td>
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Outline: Are we close to a pharmacological therapy for Celiac Disease?

• Do we need non-dietary therapies?
  Why is the GFD not enough?

• Is pharmacological therapy feasible
  Are there accessible drug targets?

• Can a pharmacological agent be approved?
  Suitable patient populations
  Relevant indications?
  Suitable outcome measures?

There are NO approved medications for Celiac disease: ALL discussions are “investigative”
Incomplete efficacy of the GFD

- >15% Persistent / frequent symptoms (non-responsive disease)
- 1 - 2% Refractory to GFD
- ~30% of adults on GFD for celiac disease for ≥5 years have ongoing partial villous atrophy on biopsy
- Strict GFD difficult to maintain
  - At social events
  - Eating outside the home
    - Travelling
    - Restaurants & cafeterias
    - Take-out
    - At school or college
  - For the elderly
  - For the illiterate
  - For those with mental or psychological impairment

70% of Celiac Disease Patients Report Gluten Exposures on GFD

- No intentional or known inadvertent lapses: 30%
- No intentional, some inadvertent lapses: 30%
- Intentional and known inadvertent lapses: 28%
- Intentional lapses but not known inadvertent lapses: 12%

Reported intentional and inadvertent gluten consumption (n=269)

“DOGGIE BAG” Study

Determination Of Gluten Grams Ingested and Excreted By Adult eating Gluten-free

- Prospective study
- 21 Manitoba Celiac Disease cohort subjects (& 3 controls on a normal diet)
- 24 months on GFD (prior to follow-up biopsy)
- 10-day sample & data collection period
  - 25% of all food (days 1-7)
  - Minimum 4 stools
  - Urine (3 per day x 10 days)

Measuring gluten in a GFD: the oxymoron study?

Silvester JA, Cebolla A, Rigaux L, Dominguez R, Leffler DA, Kelly CP, Leon F, Duerksen DR, Sousa C.
Manitoba Celiac Disease Research Group, University of Seville, Biomedical Inc., Harvard Celiac Research Program
DOGGIE BAG Study
Interim analysis: (14 of 21 subjects on a “GFD”)

Gluten immunogenic peptides (GIPs) detected:

- **86% (12/14) of patients** had detectable gluten in at least one sample in a 10 day period

- **Food samples**
  - **10% overall** (25/247)
    - 3.3% >20 ppm GIPs
    - 2.0% >100 ppm GIPs

- **Stool & Urine samples:**
  - **8.5% overall** (55/647)
    - 7.5% (30/400) urine
    - 14% (8/58) stool samples

Is a GFD a fantasy?

- Normal diet
- Low gluten diet
- Very low gluten diet
- Very, very, very low gluten diet
  
GFD = Nervana

Perceived treatment burden in Celiac disease

† VAS: 0 = Very Easy  VAS †
100 = Very Difficult

ESRD: End stage renal disease (on hemodialysis) = 56.4
CD: Celiac disease = 44.9

Higher than:
• HTN: Hypertension
• GERD
• DM: Insulin dependant diabetes
• CHF: Congestive heart failure
• IBD: Inflammatory bowel disease
• IBS: Irritable bowel syndrome

*Compared with CD, p<0.001

Patient satisfaction with the GFD is low.

Satisfaction with GFD:
- Very poor: 42%
- Poor: 35%
- Average: 23%
- Good: 7%
- Excellent: 5%
The Gluten Free Diet:

“It was the best of times, it was the worst of times”

<table>
<thead>
<tr>
<th>Feature</th>
<th>Advantage/Disadvantage</th>
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<tbody>
<tr>
<td>Helped millions - over decades</td>
<td>High burden of treatment</td>
</tr>
<tr>
<td>Safe</td>
<td>Nutritional side-effects e.g. constipation, vitamin deficiency, unwanted weight gain</td>
</tr>
<tr>
<td>Efficacious</td>
<td>Limited effectiveness, especially on an “intent to treat” basis – most are not really gluten free</td>
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<tr>
<td>Non-pharmacologic</td>
<td>Not covered by insurance in many countries</td>
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<tr>
<td>Self-administered</td>
<td>Minimal medical support</td>
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<tr>
<td>The “only” treatment for CeD</td>
<td>Has stifled research &amp; development – NO other approved options</td>
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Celiac disease - poised for drug development I

- **Common:** Revised prevalence estimates
  - US ~0.02% [1/5000] revised to ~1% (~3 million)
  - Europe ~0.1% [1/1000] revised to ~1% (~7 million)

- **Pathophysiology** elucidated - Multiple treatment targets

- Need for **lifelong therapy** attractive to pharma
Patient survey on interest in medical therapy for celiac disease

- **66% were interested** (of 339 surveyed)

<table>
<thead>
<tr>
<th>Factor</th>
<th>More interested</th>
<th>Less Interested</th>
<th>P=</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt;50 yr</td>
<td>71%</td>
<td>60%</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>78%</td>
<td>62%</td>
</tr>
<tr>
<td>Restaurant use</td>
<td>Frequent</td>
<td>76%</td>
<td>58%</td>
</tr>
<tr>
<td>Satisfied with weight</td>
<td>No</td>
<td>73%</td>
<td>51%</td>
</tr>
<tr>
<td>Concerned with cost of GFD</td>
<td>Yes</td>
<td>77%</td>
<td>64%</td>
</tr>
<tr>
<td>Quality of life score</td>
<td>Lower</td>
<td>69</td>
<td>80</td>
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**Factors NOT associated:** Time since diagnosis, education level, mode of presentation or symptoms with gluten exposure.

Progress in key areas

- Elucidation of acceptable *study designs* on path to approval
- Elucidation of acceptable *outcome measures*
- Success in recruiting volunteers to participate in clinical studies to date (including 2 large Phase 2 studies)
- Robust *involvement and co-operation by all stakeholders* (patients, pharma, healthcare/research community and regulatory authorities (FDA, NIH)).

Celiac disease - poised for drug development II
Unmet medical needs, patient populations & indications

Initially as adjuncts to the GFD for:

- Refractory CeD
- Non-responsive CeD
- To minimize symptoms following inadvertent exposure
- To protect against inadvertent exposures e.g. during “high risk” dining
- To protect against inadvertent low-level exposures during “high risk” dining and so reduce the burden of following an absolutely strict GFD

Ultimate goal – to achieve “tolerance” & allow safe consumption of a normal diet.
Many steps in Celiac disease pathogenesis are well elucidated

**Gluten / gliadin**
1. Ingested
2. Survives digestion
3. Crosses gut lining
4. “Made tastier” by TTG
5. Taken up by “antigen presenting cells” (APCs)
6. Genetically encoded DQ2 or DQ8 present
7. Presented on DQ2/8
8. T cells activated
   - Inflammation
   - Antibody production
   - Tissue damage

Figure from Schuppan et al. Gastroenterol 2009; 137:1912-33
<table>
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<tr>
<th>Company</th>
<th>Agent</th>
<th>Mechanism</th>
<th>Stage</th>
</tr>
</thead>
</table>
| ALBA Therapeutics to INNOVATE | Larozatide acetate            | Tight junction regulator                                                | NRCD: Phase 2 completed  
Phase 3 planned                                                      |
| ALVINE Pharmaceuticals, Inc. | ALV003 [Glutenase combination]| Enzymes to degrade gluten in stomach & intestine                       | NRCD: Phase 2 study completed—did not meet endpoints  
Further studies planned                                                |
| BIOLINERx To IMMUNOGENX     | BL-7010                        | Oral gluten-binding polymer                                            | Phase 1/2                                                            |
| Calypso biotech             | Anti-IL-15                     | Block IL-15 induced inflammation                                      | RCD II: Phase 2                                                      |
| celimmune                   | AMG 714, Anti-IL-15            | Block IL-15 induced inflammation                                      | RCD II: Phase 2                                                      |
| COUR                        | TIMP-GLI                       | Tolerogenic Immune Modifying nanoParticle                              | Phase 1/2                                                            |
| Zedira                      | ZED 1227                       | TTG inhibitor                                                          | Phase 2 planned                                                      |
| Immusant                    | Nexvax2                        | Gluten peptide-based therapeutic vaccine                               | Phase 2                                                              |
| Institute for Protein Design | Kumamax                        | Gluten-degrading enzyme                                                | Phase 1 planned                                                      |
New medications in celiac disease
Glutenases

**Latiglutinase (formerly ALV003)**
ImmunogenX (formerly Alvine)

- Enzymatic digestion of gluten to render it non-antigenic
  Derived from bacterial & cereal (Barley) sources
- Recent Phase 2b trial in non-responsive celiac disease
  - Did not achieve primary outcome measure
    (histological improvement)

**Alternative glutenases**
e.g. Kumamax from PvP Biologics (with Takeda)

ALV003 protects against gluten challenge

Gluten challenge (3g/d x 6 weeks) Placebo versus ALV003

Villus height versus Crypt depth

Trial effect: Improved histology (Vh:Cd) in both Placebo & Treatment groups

A challenge for trials in non-responsive celiac disease

**Background & Aim:** Gluten intolerance leads to symptoms and small intestinal mucosal injury in patients with celiac disease. The only option in the strict lifelong exclusion of dietary gluten, which is difficult to accomplish. Many patients following a gluten-free diet continue to have symptoms and have small intestinal mucosal injury. Nonpharmacological therapies are needed. We performed a phase 2 study of the ability of latilgluterase, an orally administered mixture of 2 recombinant gluten-targeting proteases, to reduce mucosal morphometric measures in biopsy specimens from patients with celiac disease. **Methods:** We performed a double-blind, placebo-controlled, dose-ranging study to assess the efficacy and safety of latilgluterase in 49 patients with celiac disease (with moderate or severe symptoms) in North America and Europe, from August 2013 until December 2014. Participants reported following a gluten-free diet for at least 1 year before the study began. Patients with documented moderate or severe symptoms and villous atrophy (villus height/crypt depth ratio of <2.0) were assigned randomly to groups given placebo or 50, 100, 200, 400, or 900 mg latilgluterase daily for 12 or 24 weeks. Subjects completed the Celiac Disease Symptom Diary each day for 28 days and underwent an upper gastrointestinal endoscopy with duodenal biopsies of the distal duodenum at baseline and at weeks 12 and 24. The primary end point was a change in the villous height/crypt depth ratio. Secondary and points included numbers of intraepithelial lymphocytes, serologic test results (for levels of antibodies against tissue transglutaminase-2 and 5-glutamylcarboxypeptidase), symptom frequencies, and safety.

**Results:** In a modified intent-to-treat population, there were no differences between latilgluterase and placebo groups in change from baseline in villous height/crypt depth ratio, numbers of intraepithelial lymphocytes, or serologic markers of celiac disease. All groups had significant improvements in histologic and symptom scores. **Conclusions:** In a phase 2 study of patients with symptomatic celiac disease and histologic evidence of significant duodenal mucosal injury, latilgluterase did not improve histologic and symptom scores when compared with placebo. There were no significant differences in change from baseline between groups. ClinicalTrials.gov no. NCT01917638.
Larazotide acetate

- Derived from studies of ZOT (zona occludens toxin) and its mammalian analogue Zonulin
- Regulates epithelial cell tight junction (TJ) function$^2$
- Phase 2b trial results published$^1$
- Innovate planning a Phase III program for NRCD (non-responsive celiac disease)


Figure: Alba / Innovate Pharmaceuticals
Larazotide Acetate Reduces CeD Symptoms on a GFD

Many steps in Celiac disease pathogenesis are well elucidated

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8. **Gluten-responsive T cells activated**
   - Inflammation
   - Antibody production
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Figure from Schuppan et al. *Gastroenterol* 2009; 137:1912-33
“Stolen therapy” examples:

- Enteric-coated budesonide (Entocort) for:
  - NRCD
  - RCD I
  - RCD II
  - Inadvertant gluten exposure
    - “the immediately after pill”
- Small intestinal release mesalamine (Pentasa)
- Systemic steroids
- Immunosuppresants: e.g. Azathioprine / 6MP
- Biologics (anti-TNF)
- Chemotherapeutics e.g. Cladribine in RCDII

Figure from Schuppan et al. Gastroenterol 2009; 137:1912-33
Q: Are we close to a pharmacological therapy for Celiac Disease?
A: We are closer - but we’re not there yet

- Therapy beyond the GFD is wanted & needed
- The stage is set
  - Common, chronic disorder
  - Current treatment imperfect and burdensome
  - General agreement between patients, researchers, FDA and pharma that new treatments should be developed
- Some years before 1st approval (successful phase 3 study awaited)
- Initially therapy will be an adjunct to the GFD (will not replace it)
- The next stage is a search for CURE – by establishing “immune tolerance to gluten”
  - A “game changer” - pioneering prevention & cure of other auto-immune disorders with less clear disease pathogenesis
OUR MISSION
The NASSCD is the North American society of medical, scientific and allied health professionals in the field of celiac disease. The organization's overall mission is to advance the fields of celiac disease and gluten-related disorders by fostering research and by promoting excellence in clinical care, including diagnosis and treatment of patients with these conditions.

APPLICATION PROCEDURE
Becoming a NASSCD member is a two-step process:

1. Complete the online application and pay your dues*.

2. The NASSCD Executive Council reviews and approves applications monthly. You will receive a notification of status after your application has been reviewed. *Please note: If your application is not approved, you will receive a full refund of your dues payment.

Join now at www.NASSCD.org!