Are we close to a pharmacological therapy for Celiac Disease?

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CELIAC RESEARCH PROGRAM
HARVARD MEDICAL SCHOOL

Conflict of Interest Disclosure (over the past 24 months)

Commercial or Non-Profit Interest	Relationship
Harvard Medical Faculty Physicians **Celiac Center at BIDMC, Boston** **Harvard Medical School - Celiac Research Program**	**Faculty member, employee** **Co-founder & Medical Director** **Co-founder**
North American Society for the Study of Celiac Disease	**Committee member, President-elect**
Foundation for Celiac Disease Outcomes Measures (FCDOM)	**Co-founder, Secretary**
Current Opinion in Gastroenterology	Editor in Chief
Celimmune	Scientific advisory board member
Cour Pharma	Scientific advisory board member, Stockholder
Glutenostics	Scientific advisory board member, Stockholder
Innovate	Scientific advisory board member
ImmunogenX	Scientific advisory board member
Takeda Pharmaceuticals	Scientific advisory board member

CanMEDS Roles Covered

X	**Medical Expert** (as *Medical Experts*, 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. *Medical Expert* is the central physician Role in the CanMEDS Framework and defines the physician's clinical scope of practice.)
	Communicator (as Communicators, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)
X	**Collaborator** (as *Collaborators*, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)
X	**Leader** (as *Leaders*, 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.)
X	**Health Advocate** (as *Health Advocates*, 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.)
X	**Scholar** (as *Scholars*, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)
	Professional (as *Professionals,* 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.)

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

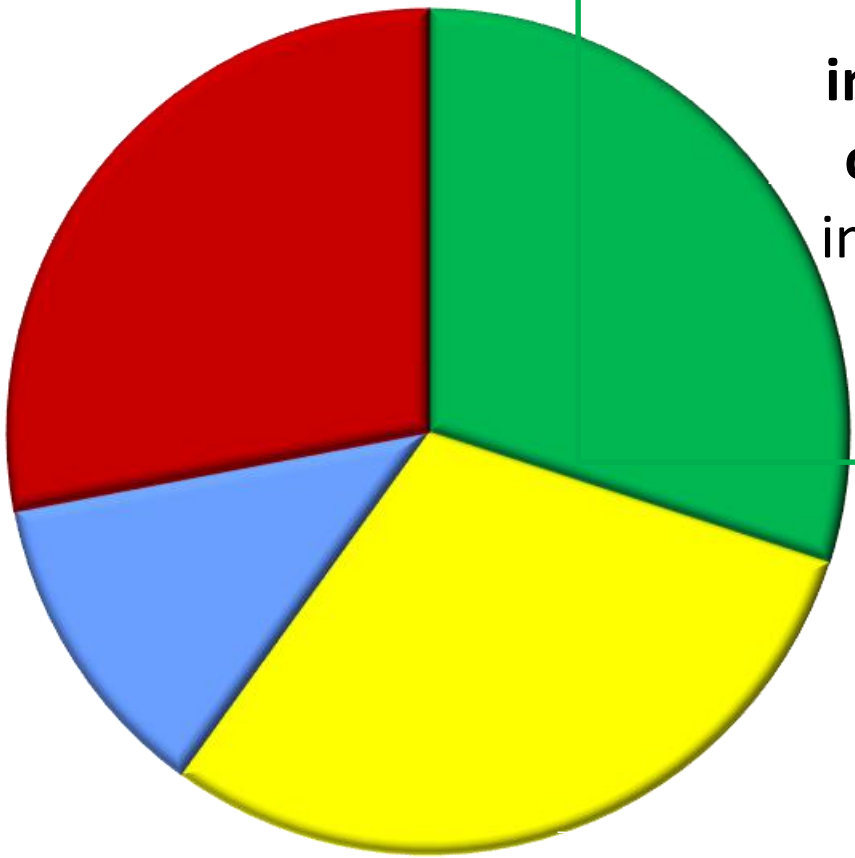
Leffler DA, Dennis M, Hyett B, Kelly E, Schuppan D, Kelly CP. Etiologies and Predictors of Diagnosis in Nonresponsive Celiac Disease. J Clin Gastroenterol Hepatol 2007;5:445-450.

Kelly CP, Bai JC, Liu E, Leffler DA. Advances in diagnosis and management of celiac disease. Gastroenterology. 2015;148:1175

70% of Celiac Disease Patients Report Gluten Exposures on GFD

Intentional and known inadvertent lapses **28%**

Intentional lapses but not known inadvertent lapses **12%**



No intentional or known inadvertent lapses **30%**

No intentional, some inadvertent 30%

Reported intentional and inadvertent gluten consumption (n=269)

Hall NJ, Rubin GP, Charnock A, Intentional and Inadvertent Non Adherence in Adult Coeliac Disease. A Cross-Sectional Survey Appetite 68:56-62, 2013

“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, Biomedal 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

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, Biomedal Inc., Harvard Celiac Research Program

Perceived treatment burden in Celiac disease

† VAS: 0 = Very Easy

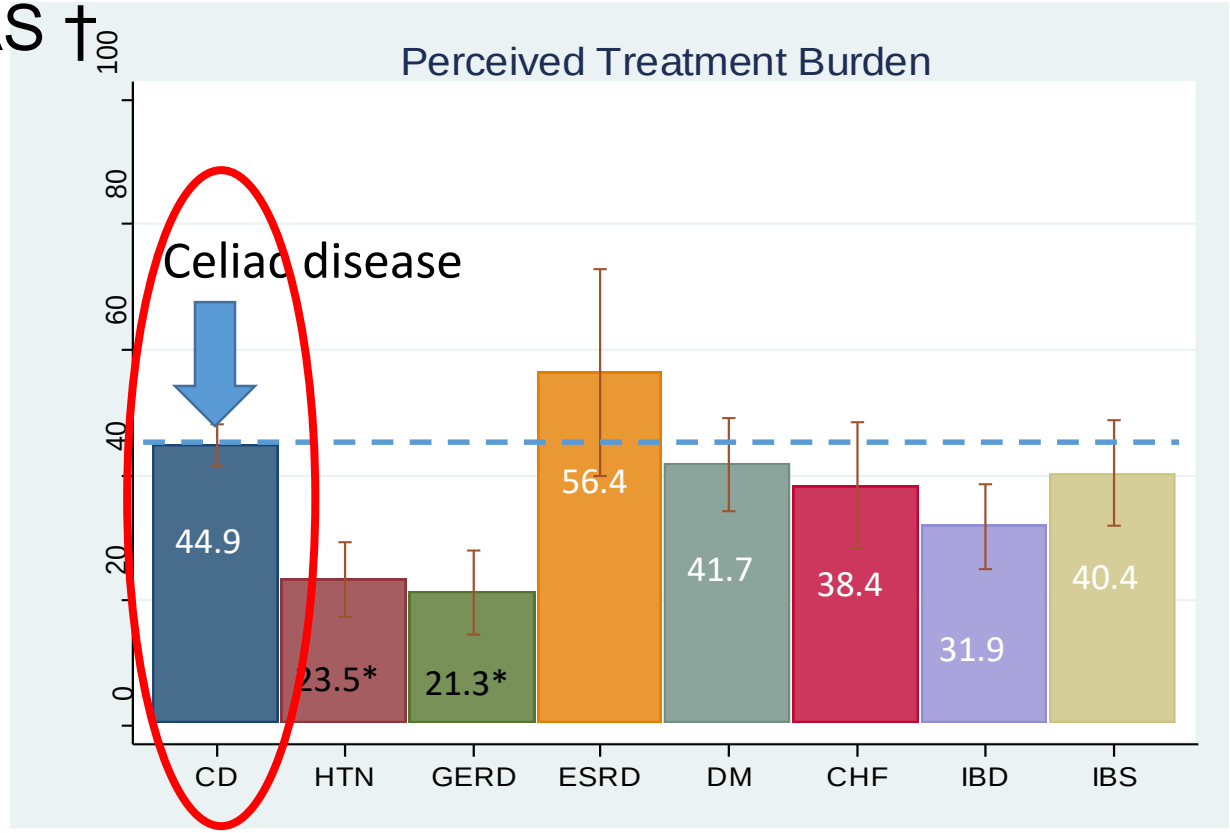
100 = Very Difficult

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

CD: Celiac disease = 44.9

Higher than:

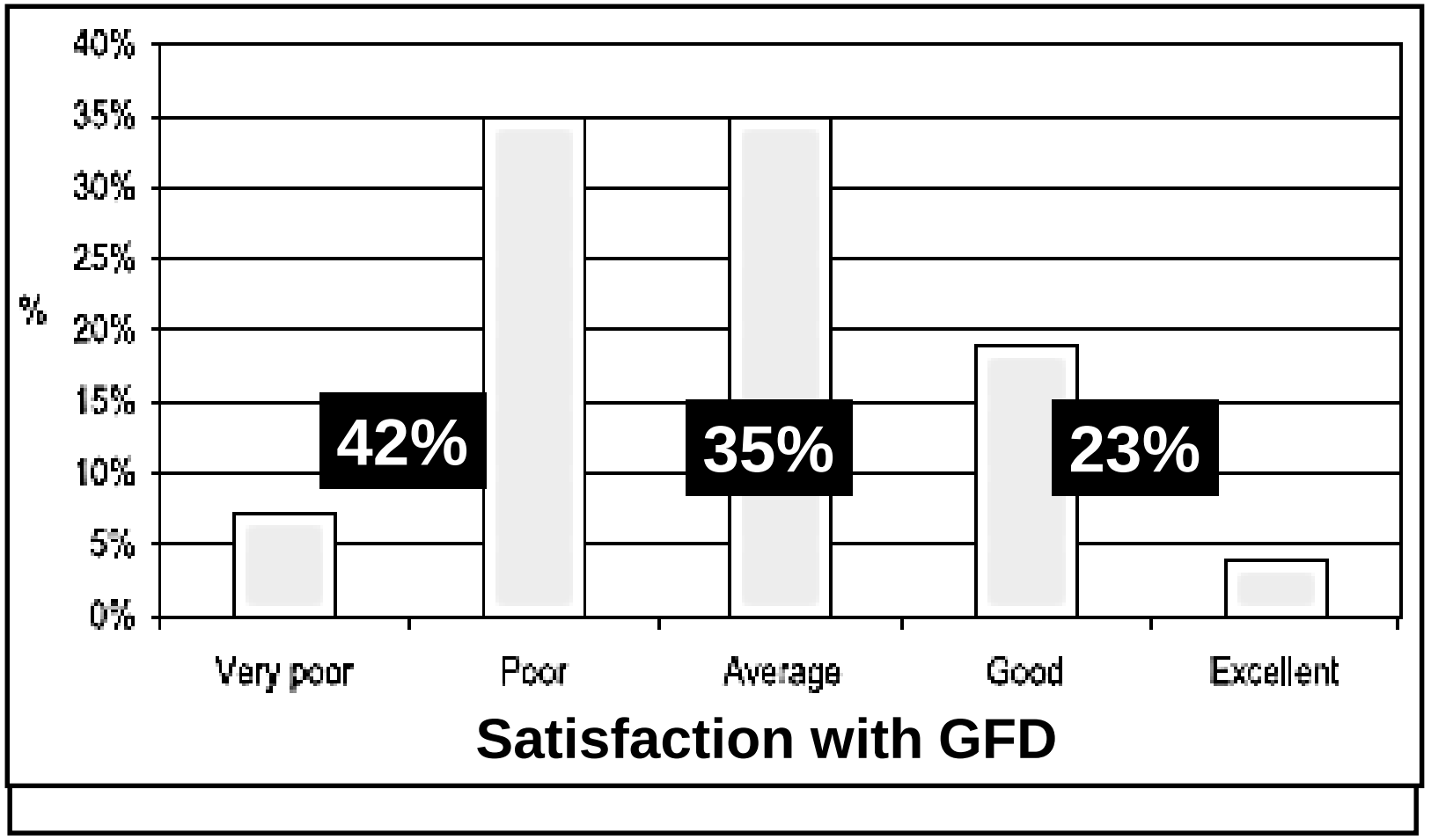
- HTN: Hypertension
- GERD
- DM: Insulin dependant diabetes
- CHF: Congestive heart failure
- IBD: Inflammatory bowel disease
- IBS: Irritable bowel syndrome



*Compared with CD, p<0.001

Shah S et al. Treatment burden in Celiac disease. Am J Gastroenterol. 2014;109:1304-11.

Patient satisfaction with the GFD is low



Sanders JGLD 2011

The Gluten Free Diet:

"It was the best of times,	*it was the worst of times"*
Helped millions - over decades	**High burden of treatment**
Safe	Nutritional side-effects e.g. constipation, vitamin deficiency, unwanted weight gain
Efficacious	**Limited effectiveness, especially on an "intent to treat" basis – most are not really gluten free**
Non-pharmacologic	Not covered by insurance in many countries
Self-administered	Minimal medical support
The "only" treatment for CeD	**Has stiffled research & development – NO other approved options**

Charles Dickens, 1859. A Tale of Two Cities.

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)*

Factor	More interested		Less Interested		P=
Age	>50 yr	71%	60%	<50 yr	P=0.04
Gender	Male	78%	62%	Female	P=0.008
Restaurant use	Frequent	76%	58%	Not frequent	P=0.0006
Satisfied with weight	No	73%	51%	Yes	P=0.0003
Concerned with cost of GFD	Yes	77%	64%	No	P=0.02
Quality of life score	Lower	69	80	Higher	P<0.0001

Factors NOT associated: Time since diagnosis, education level, mode of presentation or symptoms with gluten exposure

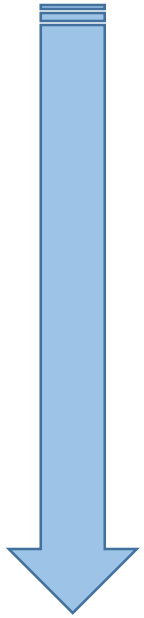
Tennyson CA, Simpson S, Lebwohl B, Lewis S, Green PH. Ther Adv Gastroenterol 2013;6:358-364

Celiac disease - poised for drug development II

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).

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

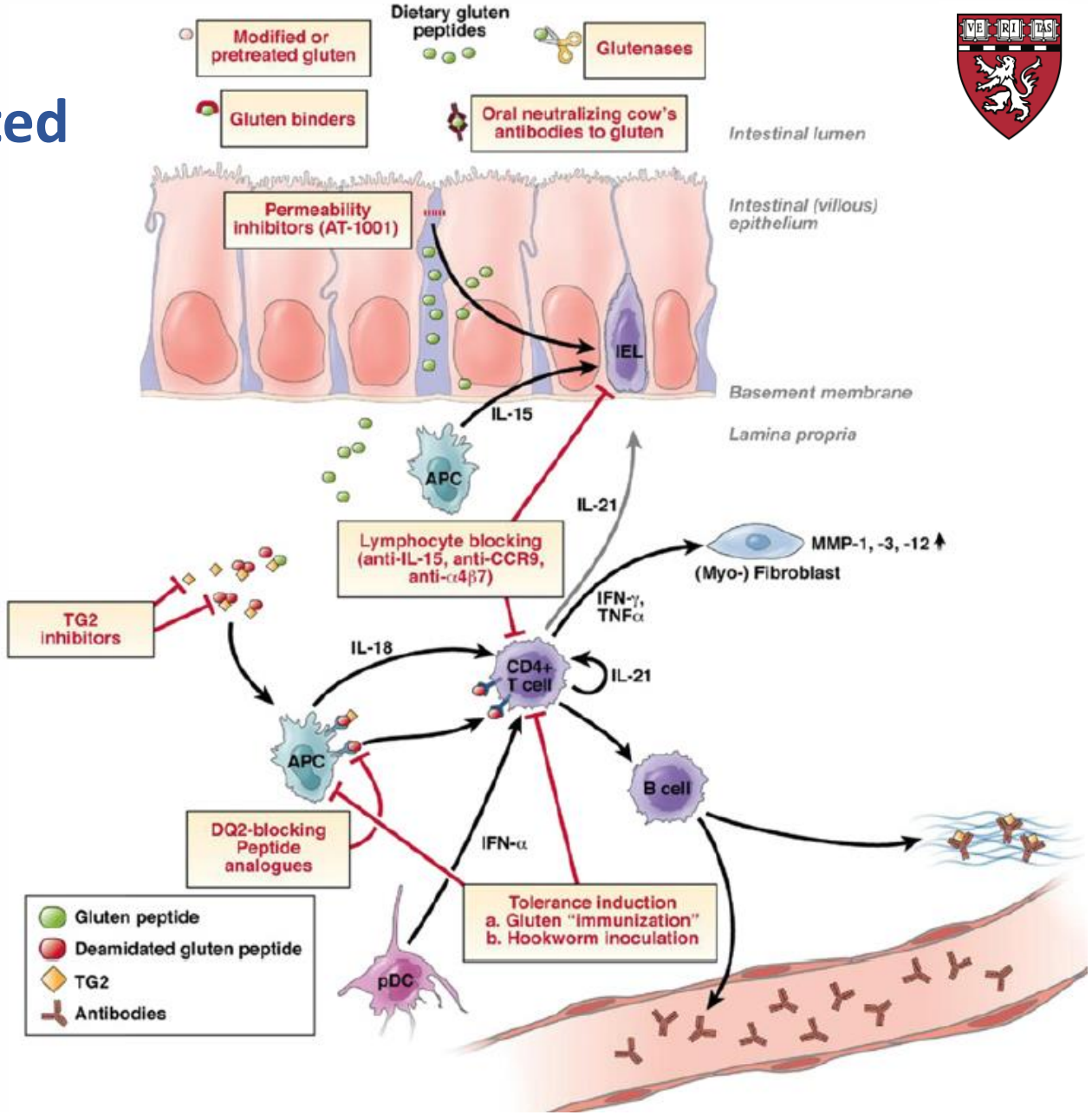


Figure from Schuppan et al. Gastroenterol 2009; 137:1912-33

Current Clinical Drug Development in Celiac disease

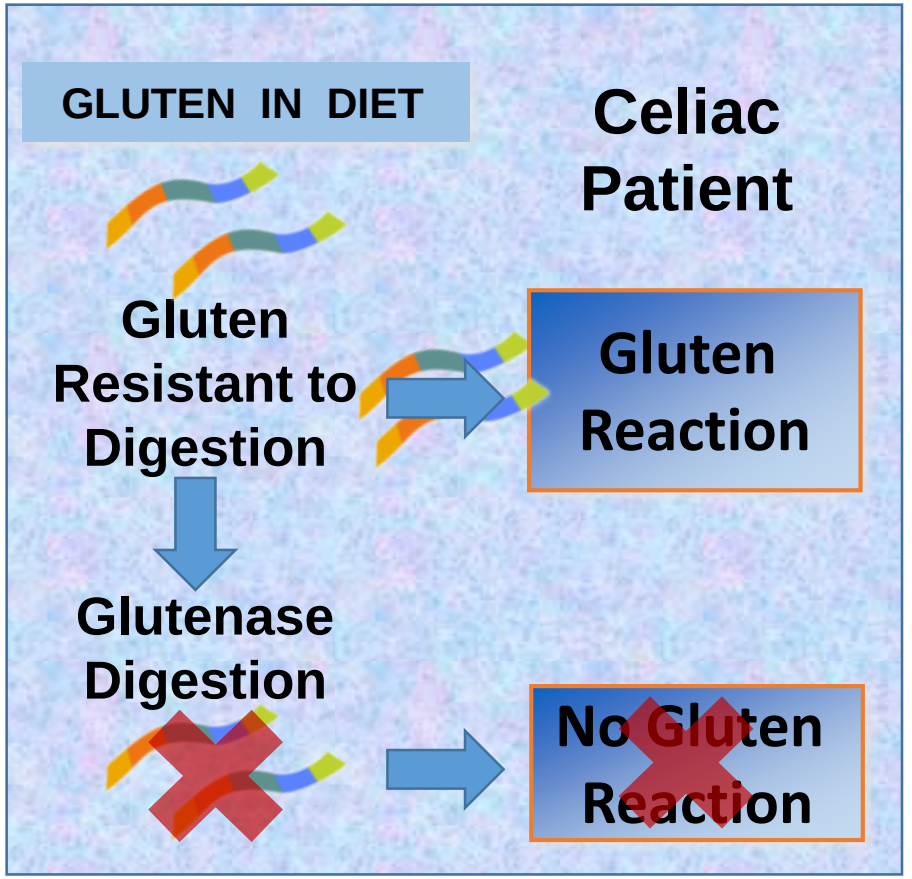
Company	Agent	Mechanism	Stage
ALBA THERAPEUTICS to INNOVATE	Larazotide acetate	Tight junction regulator	NRCD: Phase 2 completed Phase 3 planned
ALVINE PHARMACEUTICALS, INC. To IMMUNOGENX	ALV003 [Glutenase combination]	Enzymes to degrade gluten in stomach & intestine	NRCD: Phase 2 study completed–did not meet endpoints. Further studies planned
BIOLINE RX	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	Toleragenic Immune Modifying nanoParticle	Phase I/2
Zedira Falk Foundation	ZED 1227	TTG inhibitor	Phase 2 planned
ImmusanT	Nexvax2	Gluten peptide-based therapeutic vaccine	Phase 2
INSTITUTE FOR Protein Design PVP Biologics	Kumamax	Gluten-degrading enzyme	Phase I planned

New medications in celiac disease
Glutenases

Latiglutenase (formerly ALV003)
ImmunogenX (formerly Alvine)

- Enzymatic digestion of gluten to render it non-antigenic
- Two proteases (cysteine protease EP-B2 & prolyl endopeptidase (PEP).
  Derived from bacterial & cereal (Barley) sources
- Recent Phase 2b trial in non-responsive celiac disease
  - Did not achieve primary outcome measure (histological improvement)

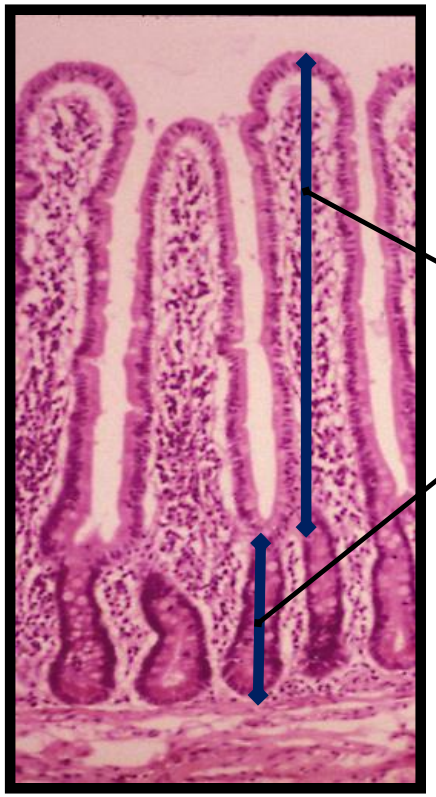
Alternative glutenases
e.g. Kumamax from PvP Biologics (with Takeda)



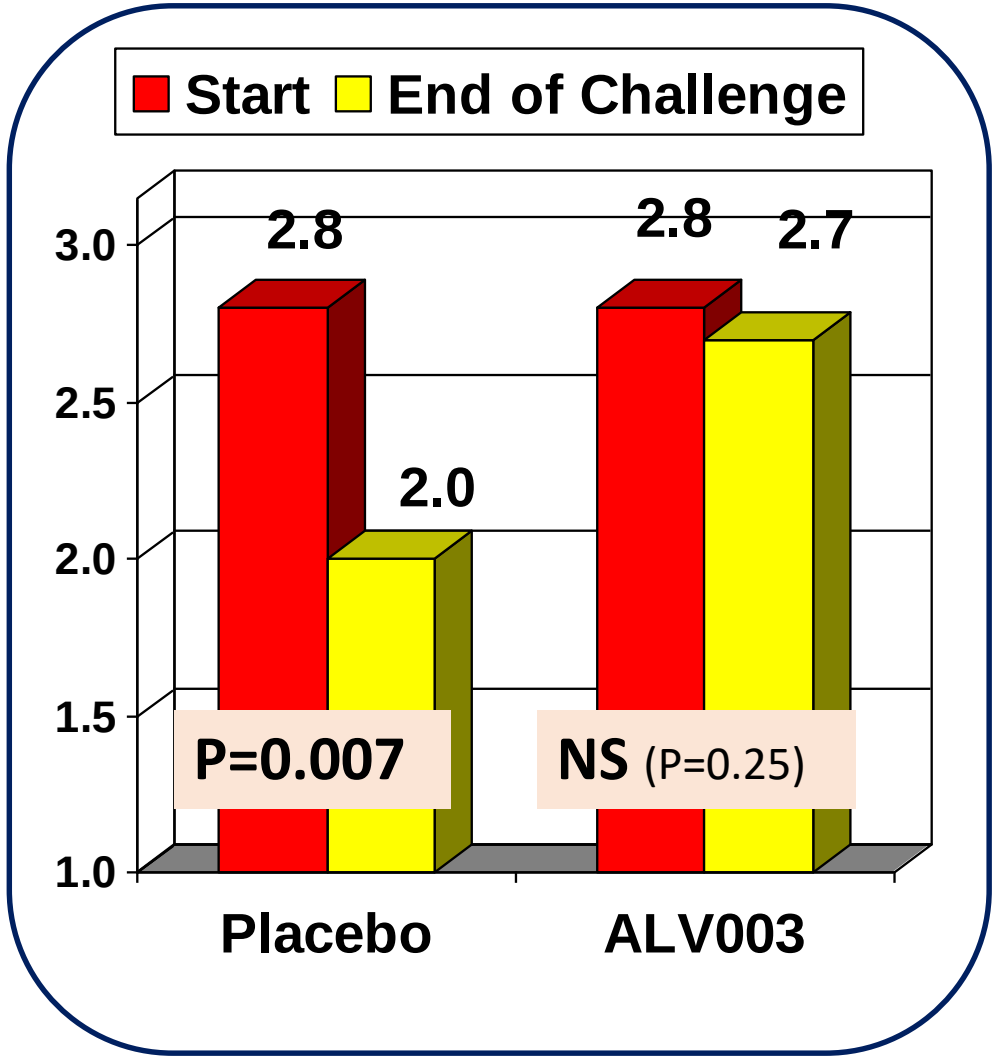
Murray JA, Kelly CP, Green PH et al. Gastroenterology. 2017;152:787-798.
Marti T et al. J Pharmacol Exp Ther 2005;312:19-26.

ALV003 protects against gluten challenge

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



Villus height *versus* Crypt depth



Lähdeaho ML et al. Gastroenterology. 2014;146:1649-58.

Phase 2 Multi-center PC-RCT

Gastroenterology 2017;152:787–798

No Difference Between Latiglutenase and Placebo in Reducing Villous Atrophy or Improving Symptoms in Patients With Symptomatic Celiac Disease

Joseph A. Murray,[1] Ciarán P. Kelly,[2] Peter H. R. Green,[3] Annette Marcantonio,[4] Tsung-Teh Wu,[5] Markku Mäki,[6] and Daniel C. Adelman,[4] on behalf of the CeliAction Study Group of Investigators

[1]Department of Gastroenterology and Hepatology, [5]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota; [2]Celiac Center, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; [3]Columbia University College of Physicians and Surgeons, New York, New York; [4]Alvine Pharmaceuticals, San Carlos, California; [6]School of Medicine, University of Tampere and Tampere University Hospital, Tampere, Finland

BACKGROUND & AIMS: Gluten ingestion leads to symptoms and small intestinal mucosal injury in patients with celiac disease. The only option is 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. Nondietary therapies are needed. We performed a phase 2 study of the ability of latiglutenase, 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 latiglutenase in 494 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 (villous height:crypt depth ratio of ≤2.0) were assigned randomly to groups given placebo or 100, 300, 450, 600, or 900 mg latiglutenase 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 biopsy 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 end points included numbers of intraepithelial lymphocytes, serology test results (for levels of antibodies against tissue transglutaminase-2 and deamidated gliadin peptide), symptom frequencies, and safety. **RESULTS:** In a modified intent-to-treat population, there were no differences between latiglutenase 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, latiglutenase 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: NCT01917630.

Keywords: Pathology; Healing; Inflammation; Treatment.

Celiac disease is an acquired chronic immune disorder occurring in individuals genetically susceptible to dietary gluten. It affects 1%–2% of the population[1–7] and is characterized by an inflammatory reaction that is accompanied by atrophy of the mucosal villi and hypertrophy of crypts.[8] Lifelong avoidance of dietary gluten is currently the only treatment option.[9] The daily intake of gluten is approximately 15–20 g in the typical Western diet.[10–12] Celiac disease has a wide range of clinical manifestations that can include acute gastrointestinal (GI) disturbances, chronic GI symptoms, malabsorption, or weight loss.

For patients with celiac disease, lifelong gluten exclusion needs to be followed strictly to reduce the risk of complications, including bone disorders, infertility, cancer, and an increase in overall mortality.[5,9,13–15] However, following a completely gluten-free diet (GFD) is challenging; even highly motivated patients are affected by inadvertent or background exposure to gluten, resulting in ongoing damage in the small intestine.[16,17] Such persistent injury can result in excess morbidity and/or mortality.[17,18] Thus, there is a need for nondietary therapies to be developed for celiac disease.[19]

The glutenase latiglutenase (formerly ALV003), is an orally administered, fixed-dose (1:1 ratio by weight) mixture of 2 gluten-targeting proteases (ALV001 and ALV002): ALV001 is a modified recombinant version of cysteine endoprotease B, isoform 2 from barley (*Hordeum vulgare*), and ALV002 is a modified recombinant version of a prolyl endopeptidase from the bacterium *Sphingomonas capsulata*. Gluten has a high proline and glutamine content, which makes it resistant to proteolysis by gastric,

Abbreviations used in this paper: AE, adverse events; ANCOVA, analysis of covariance; CDSD, celiac disease symptom diary; DGP, deamidated gliadin peptide; GFD, gluten-free diet; GI, gastrointestinal; ICDSQ, Impact of Celiac Disease Symptoms Questionnaire; IEL, intraepithelial lymphocyte; MITT, Modified Intent-to-Treat; PGI-S, Patient Global Impression-Symptoms; PRO, patient-reported outcome; SF-12, Short-Form 12; TG2, tissue transglutaminase-2; Vh:Cd, villous height to crypt depth ratio.

Most current article

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2016.11.004

Trial effect:

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

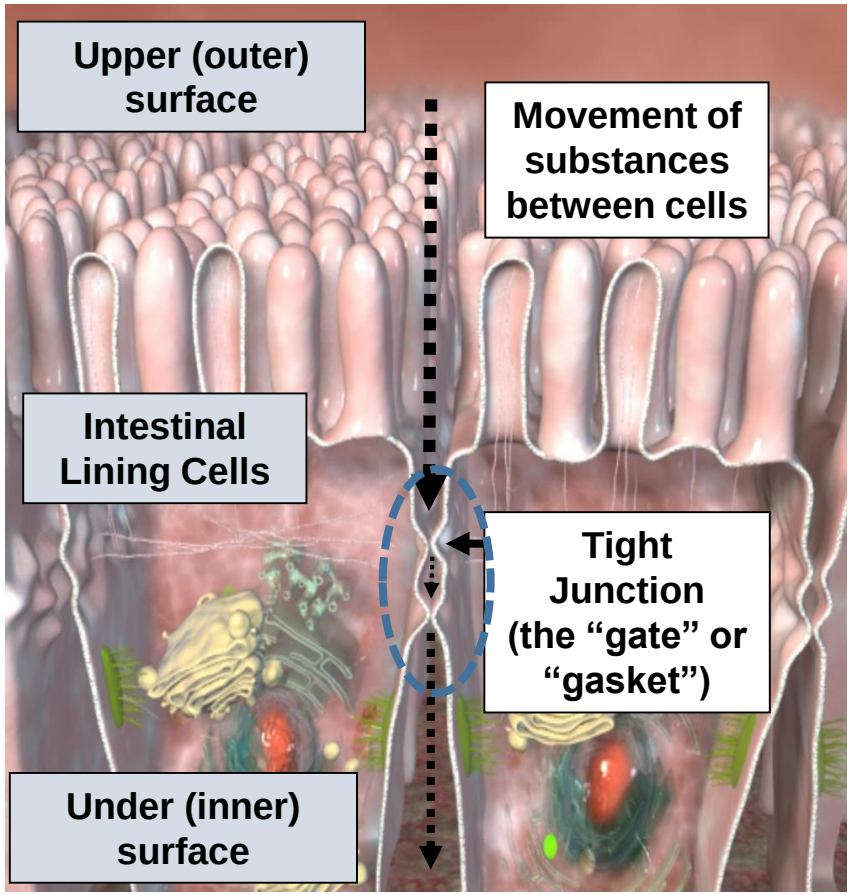
A challenge for trials in non-responsive celiac disease

RESULTS: In a modified intent-to-treat population, there were no differences between latiglutenase 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.

Larazotide acetate

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)



1. Gopalakrishnan S et al. Peptides. 2012;35:86-94 & 95-101
2. Leffler DA, Kelly CP, Green PH et al. Gastroenterology. 2015;148:1311-9.
Figure: Alba / Innovate Pharmaceuticals

Larazotide Acetate Reduces CeD Symptoms on a GFD

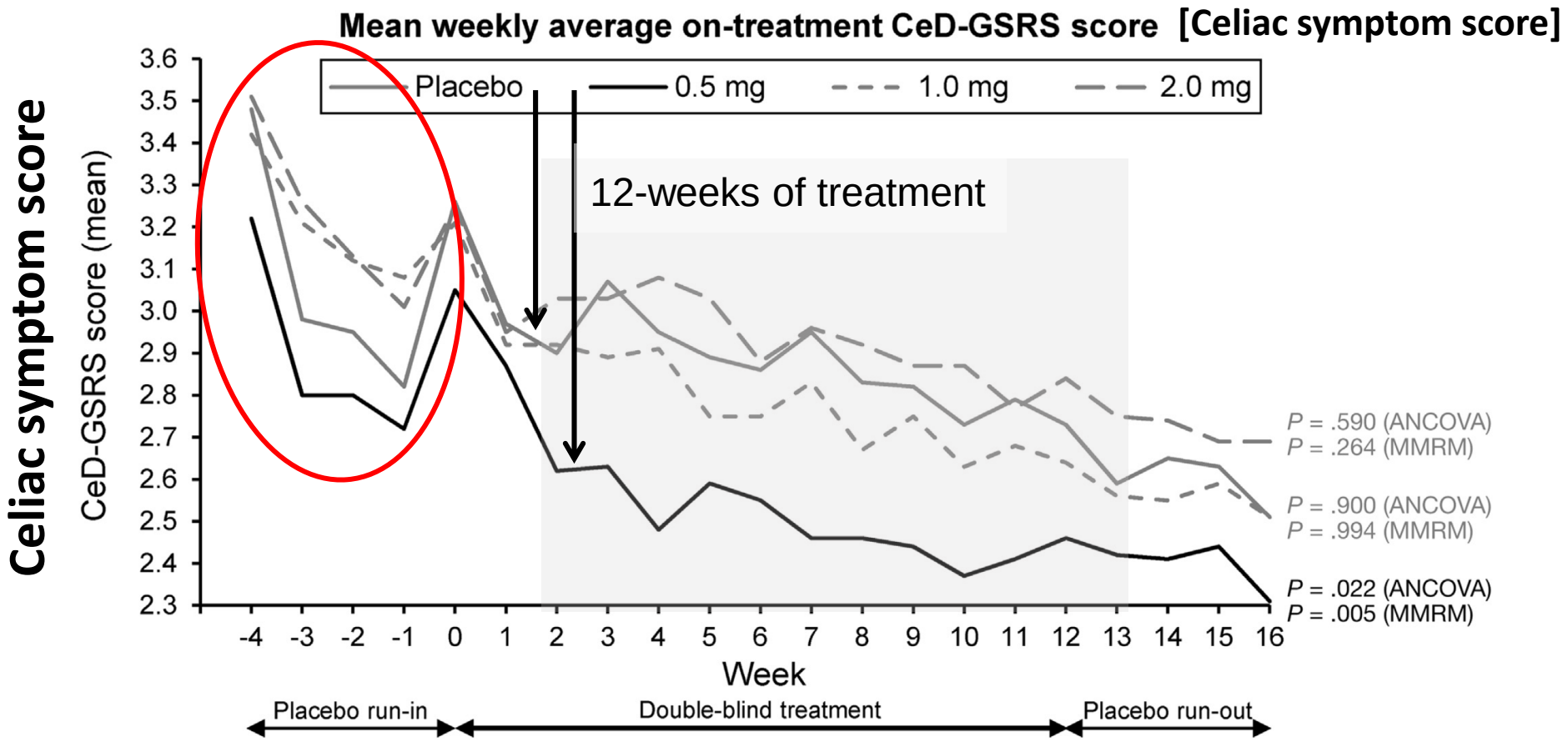


Figure 1. Primary end point: average on-treatment scores on the CeD-GSRS. The 0.5-mg larazotide acetate dose met the primary end point.

Leffler DA, Kelly CP, Green PH et al. Gastroenterology. 2015;148:1311-9.

Many steps in Celiac disease pathogenesis are well elucid

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
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8. **Gluten-responsive T cells activated**
   - Inflammation
   - Antibody production
   - Tissue damage

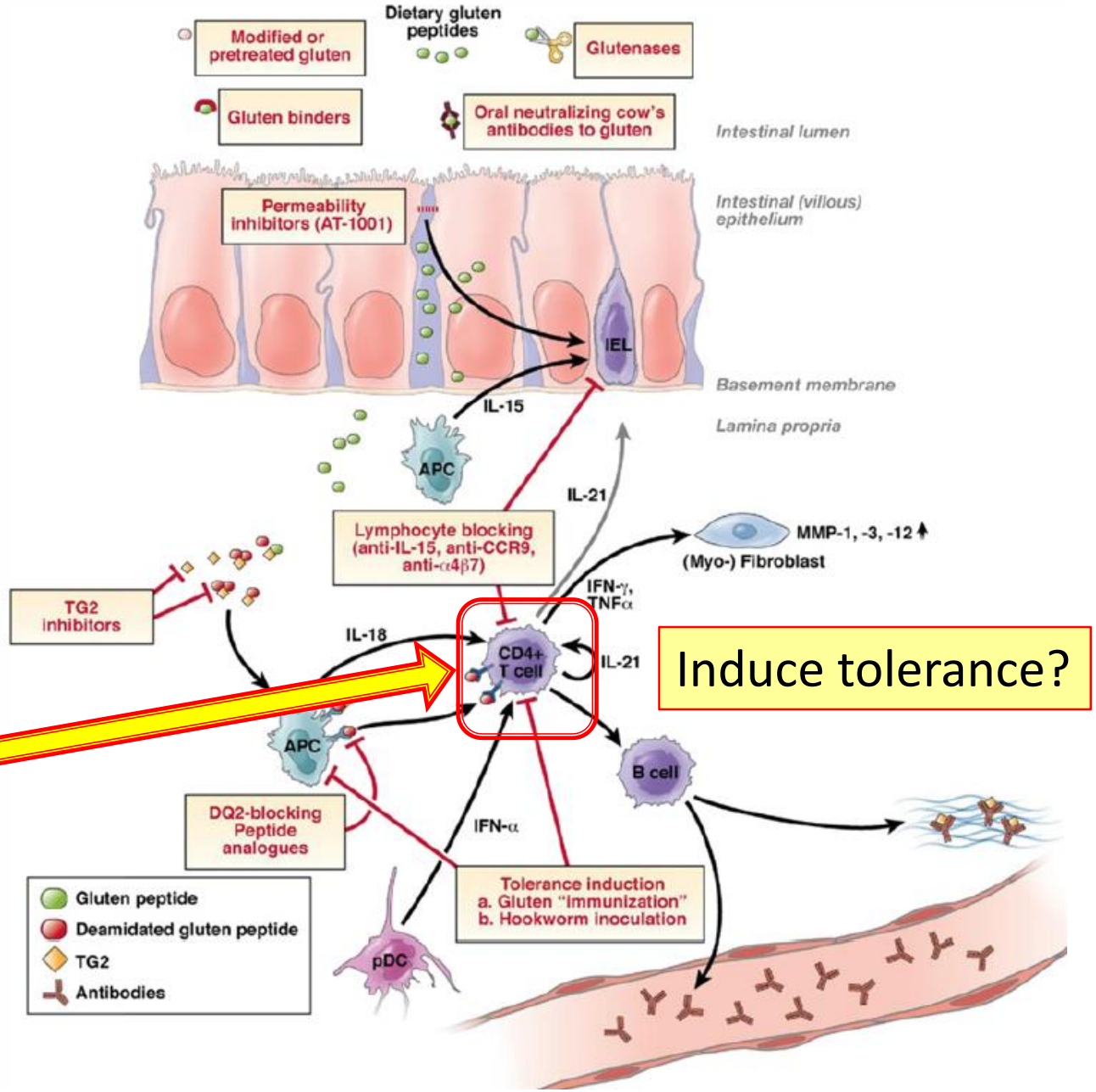

Figure from Schuppan et al. Gastroenterol 2009; 137:1912-33

“Stealing” agents from IBD, RA et al:

Gluten-responsive T cells activated

“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

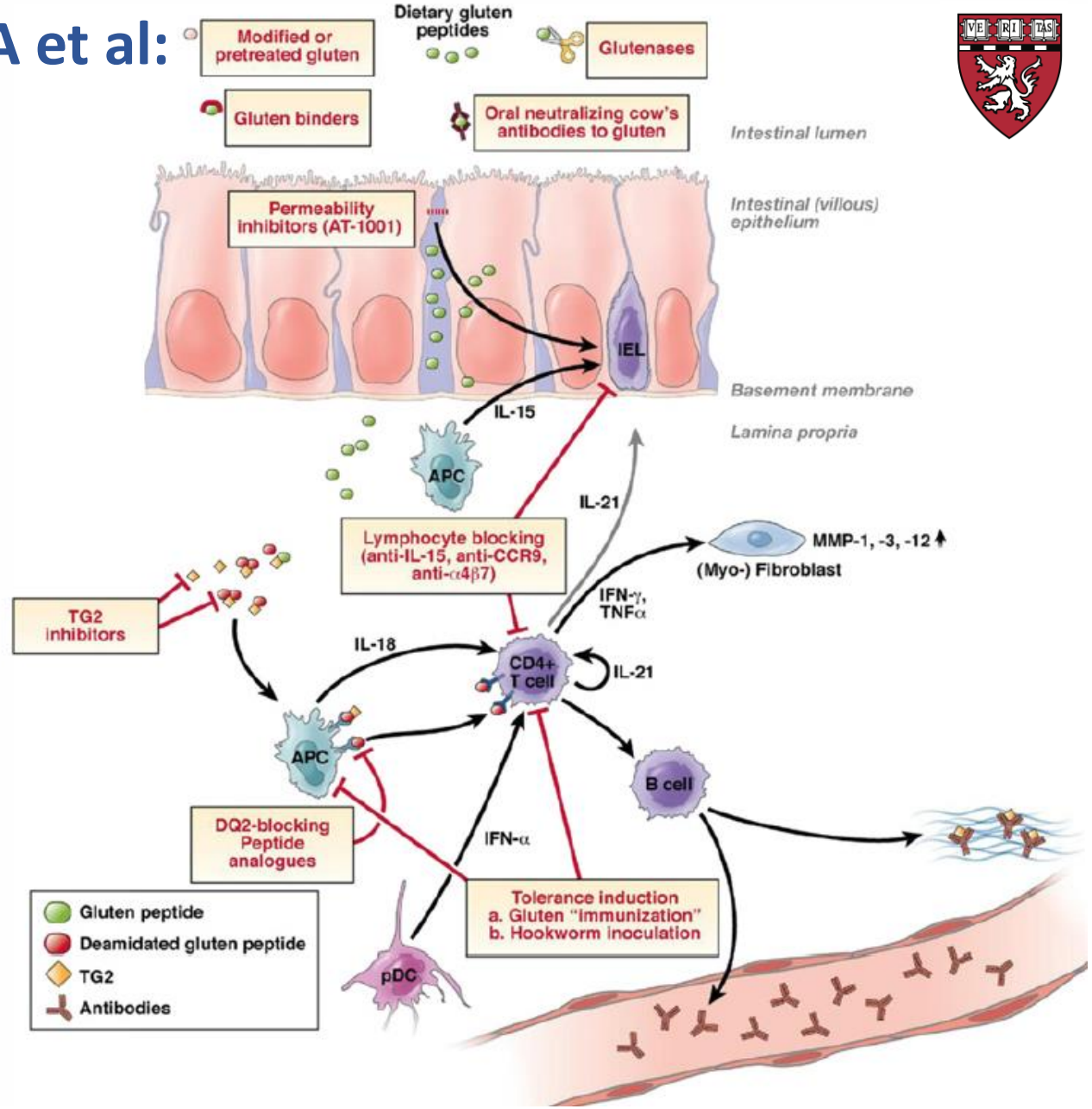

Figure from Schuppan et al. Gastroenterol 2009; 137:1912-33

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

JOIN US!

NASSCD is comprised of a diverse group of medical professionals dedicated to finding ways to treat Celiac Disease that will improve the quality of life for patients.

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. Com dues* will be earchers, and $5 at this does n

www.NASSCD.org to Join!

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.