New treatment of Celiac disease



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Goals

New therapeutic strategies in order to

- improve the quality of life .
- avoid limitations of the social relationships

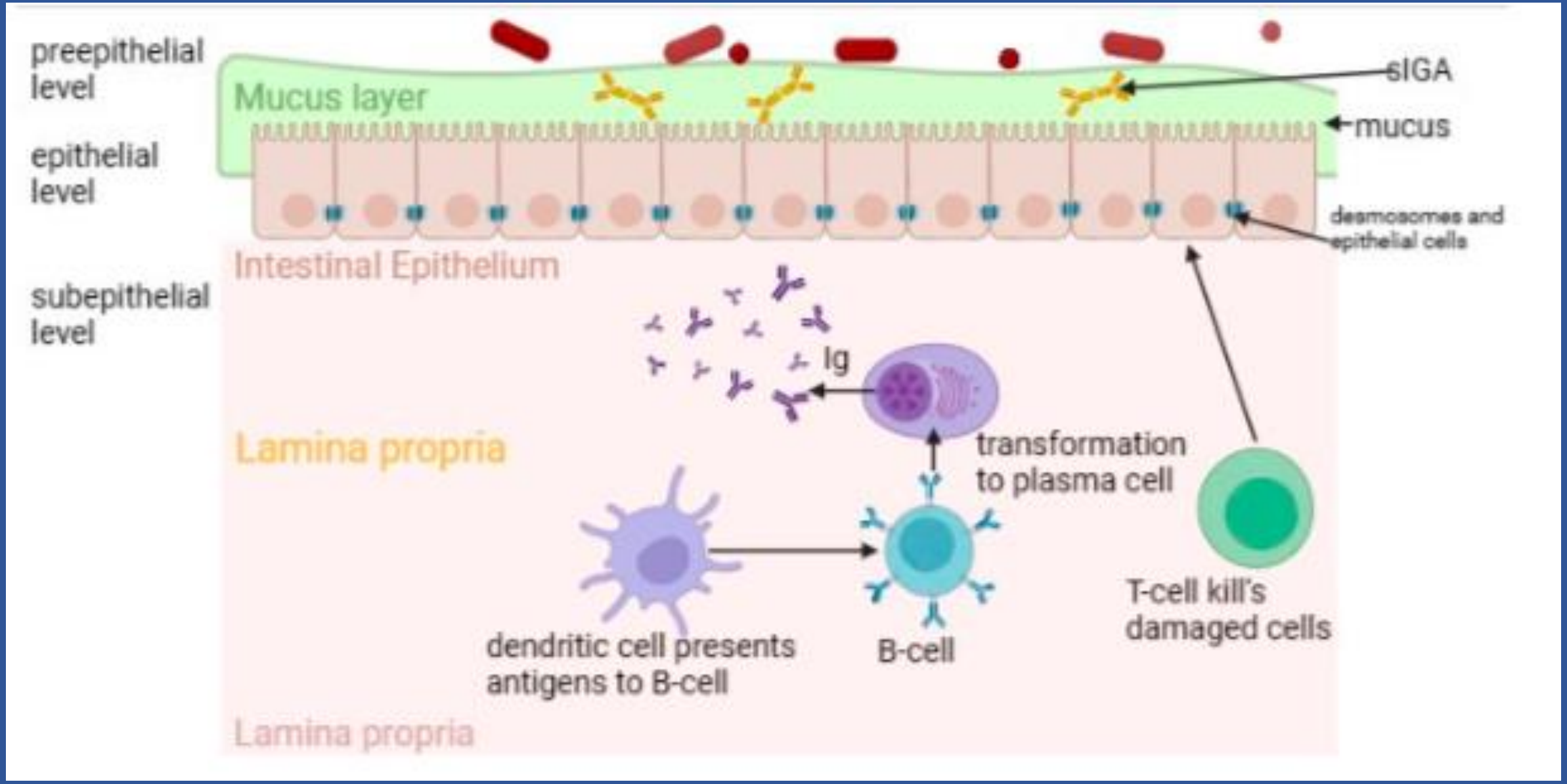
- on the other hand the lack of therapies for RCD.

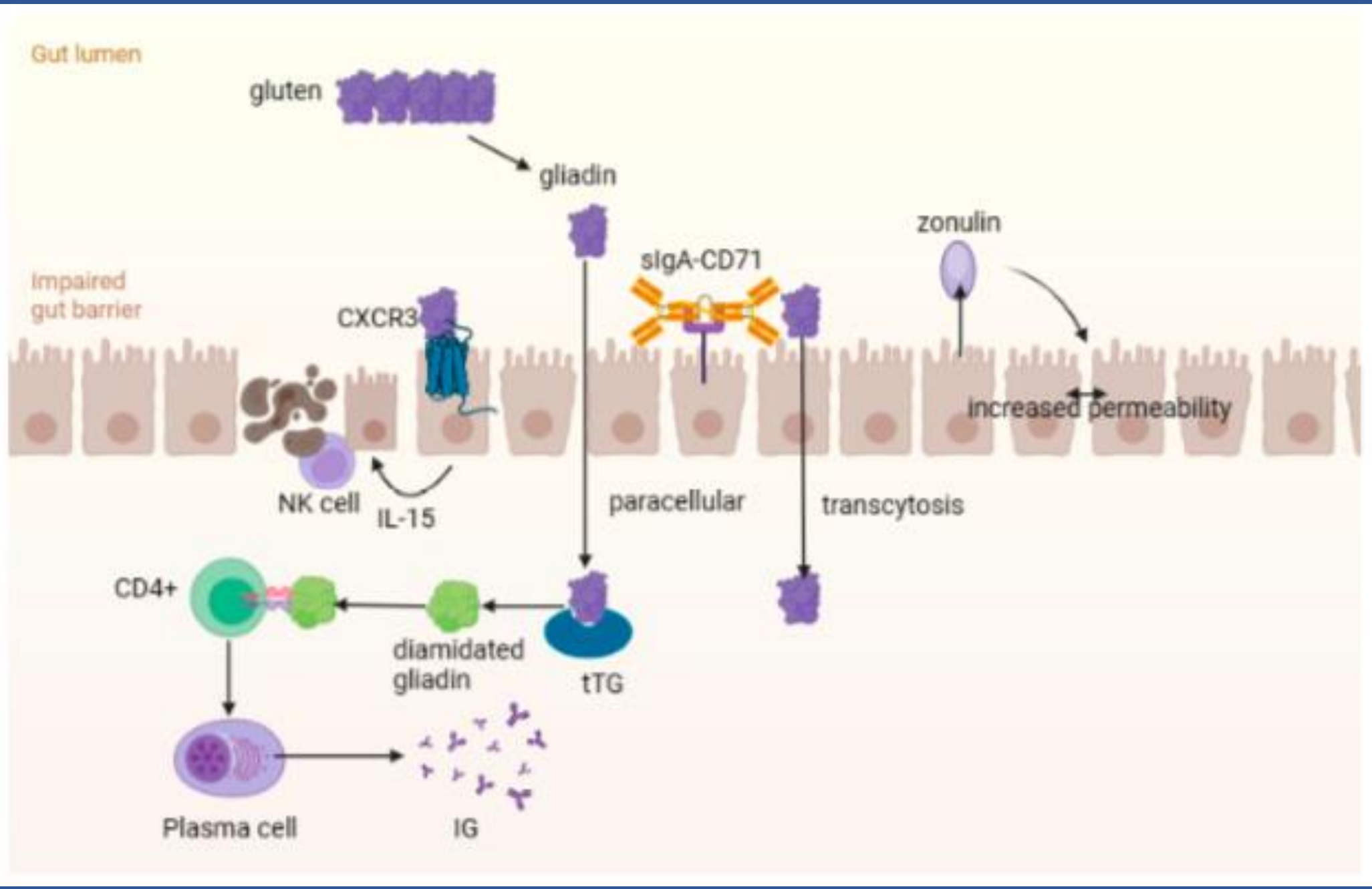
RCD if GFD were not adequate

Most common cause of residual disease activity is dietary nonadherence or inadvertent gluten exposure.

Treatment

- These can be broadly classified into luminal approaches that aim to quantitatively reduce the load of gluten available to trigger the immune response and
- Qualitative approaches that aim to induce gluten tolerance.
- A third category, encompass immunomodulators, biologics (e.g., anti-IL-15, anti-CD52), and chemotherapy (e.g., cladribine)


preepithelial level
epithelial level
subepithelial level
Mucus layer
sIGA
mucus
desmosomes and epithelial cells
Intestinal Epithelium
Ig
Lamina propria
transformation to plasma cell
T-cell kill's damaged cells
dendritic cell presents antigens to B-cell
B-cell
Lamina propria


Gut lumen
gluten
gliadin
zonulin
sIgA-CD71
Impaired
gut barrier
CXCR3
Increased permeability
NK cell
IL-15
paracellular
transcytosis
CD4+
diamidated
gliadin
tTG
Plasma cell
IG

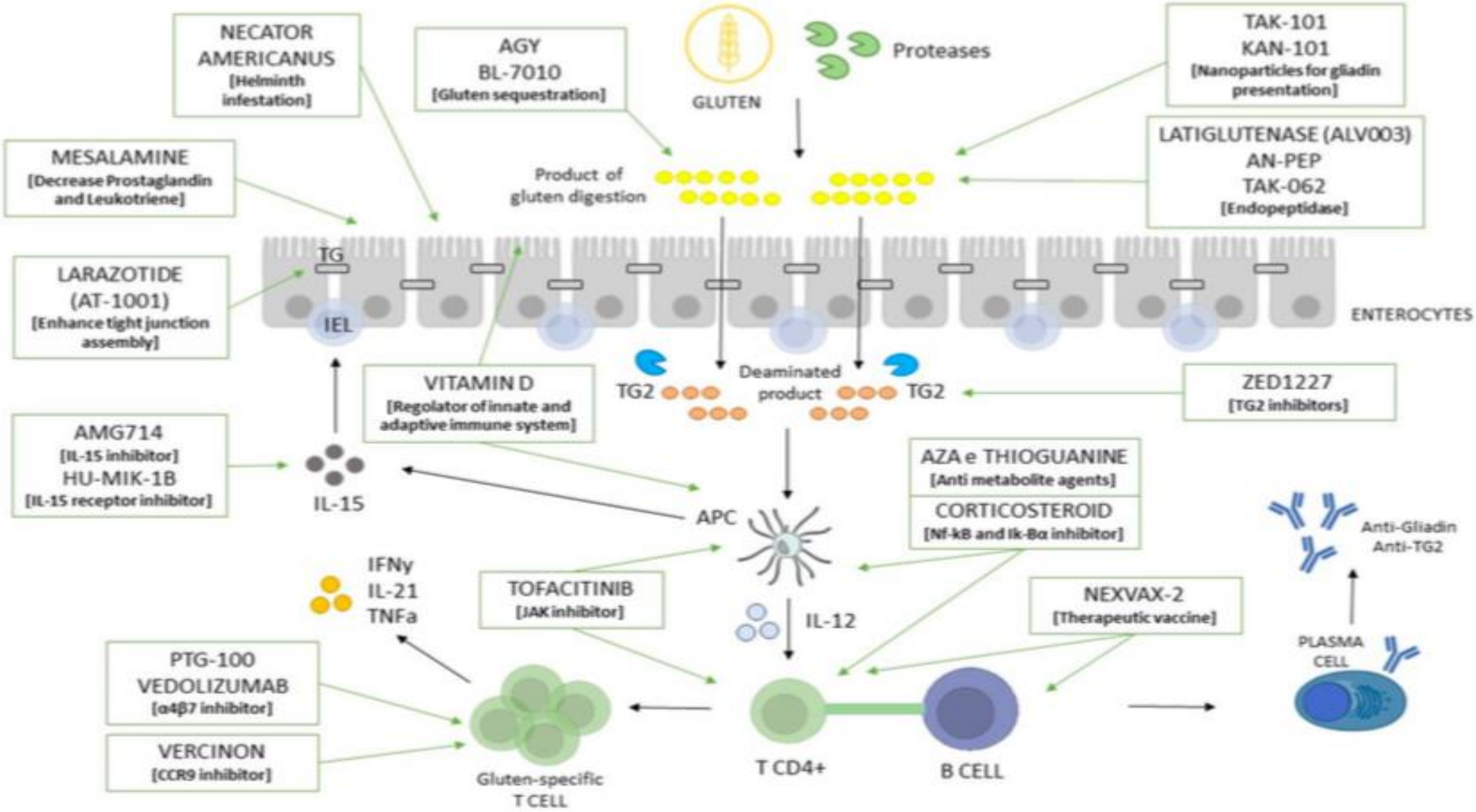
Int. J. Mol. Sci. 2023

International Journal of
Molecular Sciences

Review

Old and New Adjunctive Therapies in Celiac Disease and Refractory Celiac Disease: A Review

Marco Valvano, Stefano Fabiani, Sabrina Monaco, Mauro Calabrò, Antonio Mancusi, Sara Frassino, Claudia Rolandi, Marta Mosca, Susanna Faenza, Emanuele Sgamma, Nicola Cesaro and Giovanni Latella *


NECATOR AMERICANUS [Helminth infestation]
AGY BL-7010 [Gluten sequestration]
GLUTEN
Proteases
TAK-101
KAN-101
[Nanoparticles for gliadin presentation]
MESALAMINE [Decrease Prostaglandin and Leukotriene]
Product of gluten digestion
LATIGLUTENASE (ALV003)
AN-PEP
TAK-062
[Endopeptidase]
TG
LARAZOTIDE (AT-1001) [Enhance tight junction assembly]
IEL
ENTEROCYTES
VITAMIN D [Regolator of innate and adaptive immune system]
TG2
Deaminated product
TG2
ZED1227 [TG2 inhibitors]
AMG714 [IL-15 inhibitor]
HU-MIK-1B [IL-15 receptor inhibitor]
IL-15
APC
AZA e THIOGUANINE [Anti metabolite agents]
CORTICOSTEROID [Nf-kB and Ik-Bα inhibitor]
Anti-Gliadin
Anti-TG2
IFNγ
IL-21
TNFa
TOFACITINIB [JAK inhibitor]
IL-12
NEXVAX-2 [Therapeutic vaccine]
PTG-100
VEDOLIZUMAB [α4β7 inhibitor]
VERCINON [CCR9 inhibitor]
PLASMA CELL
Gluten-specific T CELL
T CD4+
B CELL

Tight Junction Modulation

- only drug in phase III is larazotide acetate (known as AT-1001 and INN-202), which is a synthetic, peptide that decreases intestinal permeability, enhancing tight junction

- in CD patients on a GFD, larazotide acetate reduced symptoms better than a GFD alone

- However, in 2022 a phase 3 clinical trial was suspended after an interim analysis showed no significant effectiveness

New Developments in Celiac Disease Treatment. *Int. J. Mol. Sci.* **2023**,

Transglutaminase II Inhibitors

- Transglutaminase II (TG2) inhibition blocks proliferation of T cells and prevents increase of activated T cells

- Also modulates intestinal epithelial permeability functions in vitro

A Randomized Trial of a Transglutaminase 2 Inhibitor for Celiac Disease. *N. Engl. J. Med.* **2021**, *385*, 35–45.

- Phase-II clinical trial involving 160 CD patients in remission assessed the effectiveness of the TG2 inhibitor (ZED-1227), orally administered (at a daily dose of 10, 50, or 100 mg) after 6 W of gluten challenge.
- Attenuated gluten-induced duodenal mucosal injury

- TG2 inhibitor can be effective and need more studies.

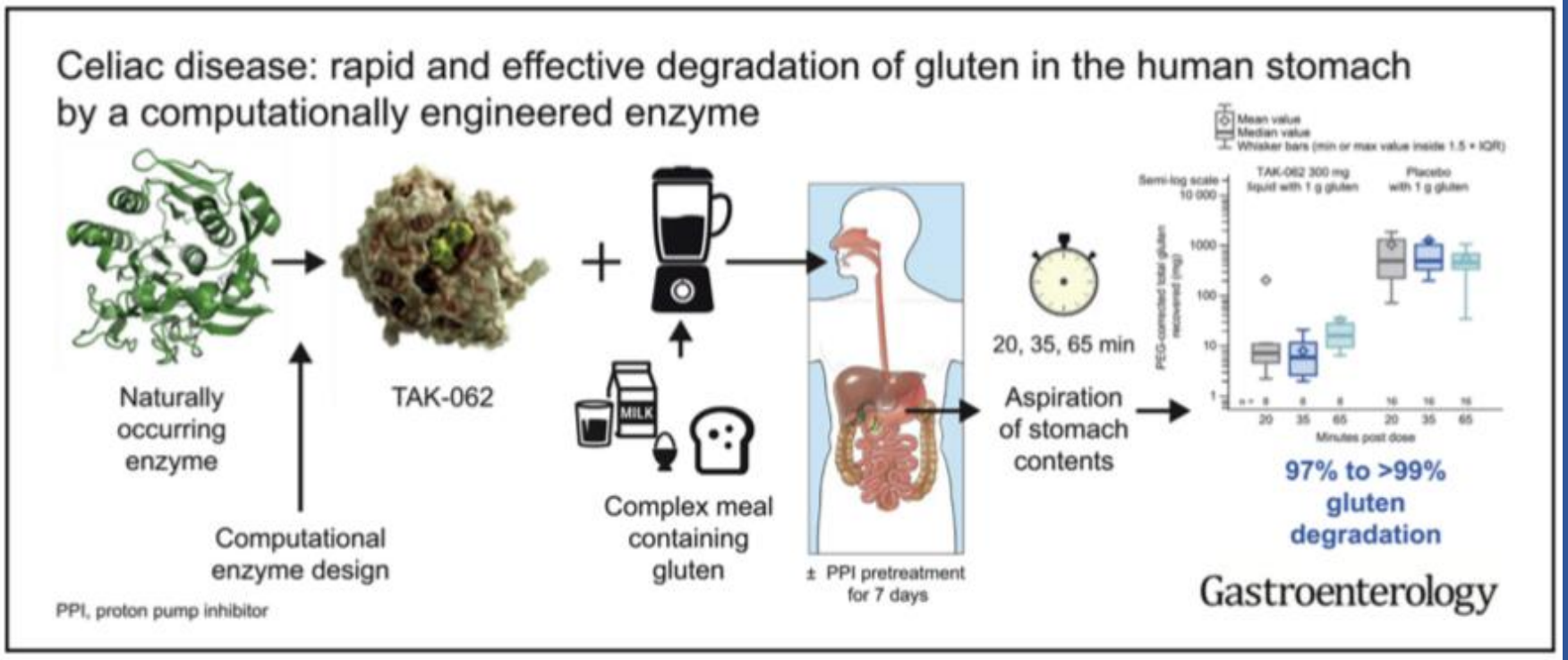
Endopeptidases

- Inactivation of gluten in the GI by peptidase.
- ALV003, or latiglutenase, is the most investigated enzyme.
- ALV003 is an orally administered mixture of two gluten-degrading proteases which are activated in the acidic environment of the stomach
- No differences between latiglutenase and placebo in reducing villous atrophy or improving symptoms in phase II trials

Gluten Degradation, Pharmacokinetics, Safety, and Tolerability of TAK-062, an Engineered Enzyme to Treat Celiac Disease

Ingrid Swanson Pultz,[1] Malcolm Hill,[1] Joanne M. Vitanza,[1] Clancey Wolf,[1] Lasse Saaby,[2] Tina Liu,[3] Peter Winkle,[4] and Daniel A. Leffler[3]

[1]PvP Biologics, Inc, San Diego, California: [2]Bioneer A/S, Hørsholm, Denmark; [3]Takeda Pharmaceuticals International Co, Cambridge, Massachusetts; and [4]Anaheim Clinical Trials, Anaheim, California



- Another phase II RCT showed symptomatic improvement and reducing intestinal mucosal damage.

- The efficacy of aspergillus niger prolyl endoprotease (AN-PEP) was studied but improvement in histology was not met in an RCT.

Gluten Degradation, Pharmacokinetics, Safety, and Tolerability of TAK-062, an Engineered Enzyme to Treat Celiac Disease. *Gastroenterology* **2021**, *161*, 81–93.e3.

- Base on evidence ,endopeptidases did not show significant effectiveness as adjunctive treatment in CD patients.

Latiglutenase Protects the Mucosa and Attenuates Symptom Severity in Patients with Celiac Disease Exposed to a Gluten Challenge. *Gastroenterology* **2022**, *163*, 1510–1521

Gluten Sequestration

- gliadin Ab and polymeric binders (AGY and BL-7010) as

sequestering gluten before its digestion into immunogenic peptides, cause fewer celiac-related symptoms and improved quality of life.

- An ongoing RCT , crossover trial are going to evaluate the safety and efficacy of AGY. This data could show the efficacy of AGY as adjunctive therapy .

AGY, a Novel Egg Yolk-Derived Anti-gliadin Antibody, Is Safe for Patients with Celiac Disease. *Dig. Dis. Sci.* **2017**,

Nanoparticles for Gliadin Presentation

- Nanoparticles for gliadin presentation, To deliver specific antigens and induce tolerance in T cells.
- TAK-101 is gliadin encapsulated in nanoparticles. In a phase II RCT, 33 CD patients completed the 14-day gluten challenge.
- TAK- 101 induced an 88% reduction in immunogenic effect and reduced changes in circulating CD4.

Gastroenterology 2021;161:66–80

CLINICAL—ALIMENTARY TRACT

TAK-101 Nanoparticles Induce Gluten-Specific Tolerance in Celiac Disease: A Randomized, Double-Blind, Placebo-Controlled Study

Ciarán P. Kelly,[1,*] **Joseph A. Murray**,[2,*] Daniel A. Leffler,[3,4] Daniel R. Getts,[5,6] Adam C. Bledsoe,[7] Glennda Smithson,[4] M. Roy First,[5] Amy Morris,[5] Michael Boyne,[5] Adam Elhofy,[5] Tsung-Teh Wu,[8] Joseph R. Podojil,[5,6] and Stephen D. Miller,[6,9] on behalf of the TAK-101 Study Group

- Nanoparticles Poly(DL-lactide-co-glycolide) (PLGA)-antigen (Ag) have been developed to deliver specific antigens that induce tolerance.

- Particle uptake by macrophage receptor (APCs) lead to anergy within T cells and activate populations of regulatory T cells.

- Nanoparticles for gliadin presentation can be promising molecules to be subjected to further studies.

TAK-101 Nanoparticles Induce Gluten-Specific Tolerance in Celiac Disease: A Randomized, Double-Blind, Placebo-Controlled Study. *Gastroenterology* **2021**, *161*, 66–80.e8.

IL-15 Signaling

- IL-15 is upregulated in active CD
- A human monoclonal Ab (AMG 714,) that binds all forms of IL-15 inhibiting their functions
- Tofacitinib, a JAK2/3 inhibitor, has demonstrated some beneficial effects in transgenic mice overexpressing human IL-15, which mimics RCD
- No evidence to support their use in CD.

Safety and efficacy of AMG 714 in adults with coeliac disease exposed to gluten challenge: A phase 2a, RCT . *Lancet Gastroenterol. Hepatol.* **2019**, *4*, 948–959.

Therapeutic Vaccine

Nexvax2, a therapeutic vaccine have three gluten peptides covering five HLA-DQ2 epitopes frequently recognized by gluten-specific T-cells .

Epitope-specific immunotherapy targeting CD4-positive T cells in coeliac disease: Two randomised, double-blind, placebo-controlled phase 1 studies. *Lancet Gastroenterol. Hepatol.* **2017**, *2*, 479–493

Therapeutic Vaccine

- Phase 1 studies showed safety of the vaccine after intradermal administration.
- Phase 2 study aimed to document the bioavailability of Nevax2 peptides after subcutaneous and intradermal dosing, and tolerability and ability of subcutaneous dosing to induce non-responsiveness to peptides

- subcutaneous and intradermal dosing of Nexvax2 had similar bioavailability ,therefore, higher subcutaneous dose , cause immune response to gluten.

- Although this vaccine could represent an interesting novelty, it has not been supported by clinical data in the current literature.

Prebiotics and Probiotics

- CD is associated with intestinal microbiota alterations.
- The administration of probiotics and prebiotics could be a promising method of restoring gut homeostasis in CD.

Clinical and Microbiological Effect of a Multispecies Probiotic Supplementation in Celiac Patients with Persistent IBS-type Symptoms. *J. Clin. Gastroenterol.* **2019**,

- Probiotics (five strains of lactic acid bacteria and bifidobacteria) in CD symptoms measured by questionnaires such as the IBS-SSS (IBS Severity Scoring System) and the GSRS (GI Symptom Rating Scale)

- oligofructose- inulin (significantly increases bifidobacterium) resulted in an improvement in consistency of stool in children on GFD

- Prolonged used, showed moderate effect on faecal microbiota.

- Evidence of treatment with probiotics evaluated in different outcomes (characteristics of microbiota, symptoms using different validate score, cytokines).

- RCTs of higher methodological quality are needed, especially regarding the outcomes measured.

Thus:

- According to the current guidelines, no drug therapy is better than GFD in CD, and the current evidence does not support any adjunctive therapy.

- In slow responders, despite the large number of studies about old and new therapies, no drugs are approved in the current guidelines.

Management of Slow Responder CD Patients

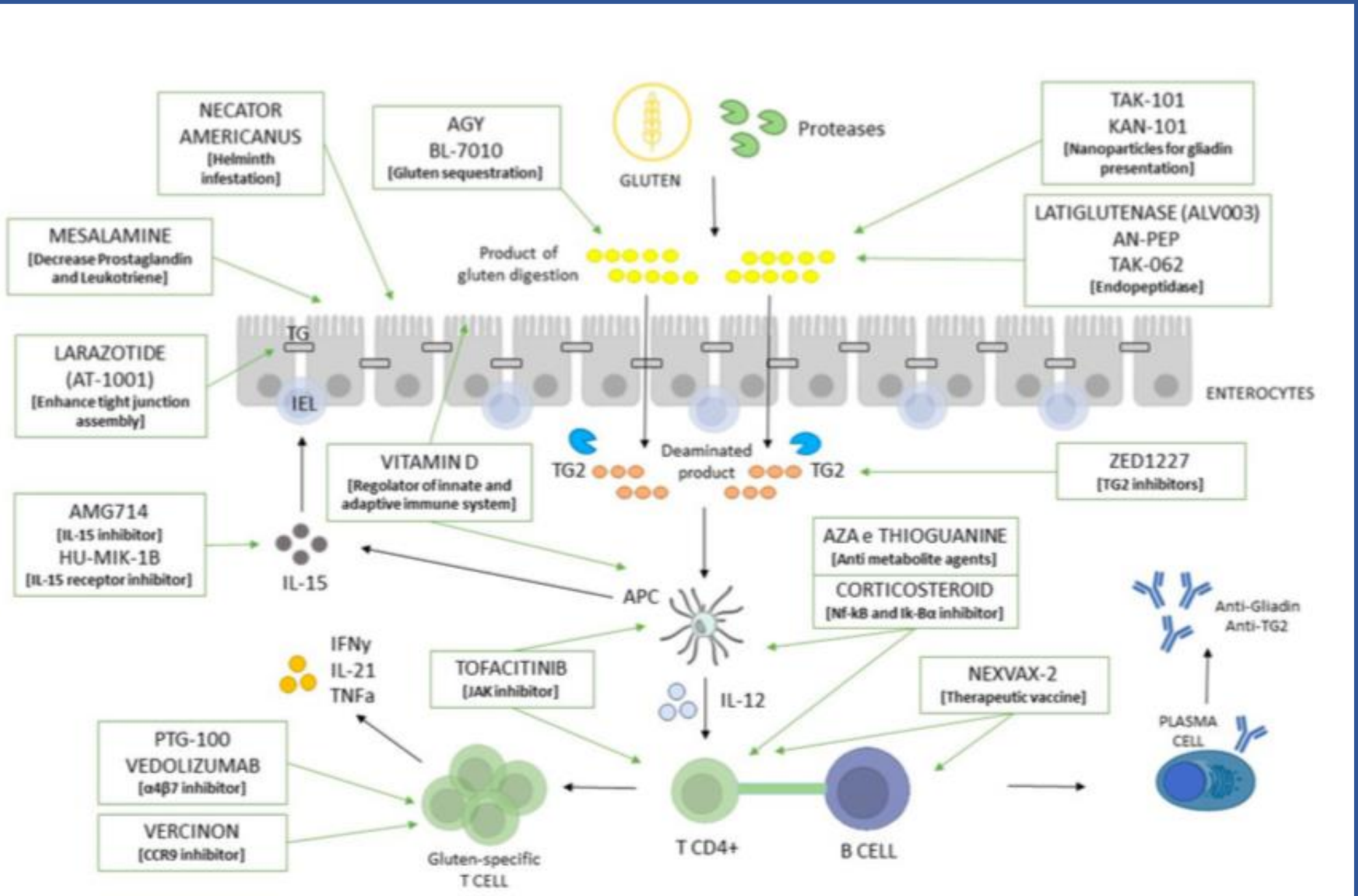
- None of the above therapies are approved in the current CD guidelines. correct management focused on reevaluation of diagnosis because alternative diseases and treatments considered.

- Inadvertent ingestion of gluten is the most common cause of slow response (35–50%).

Few therapies, may be revealed as useful adjunctive therapeutic strategies such as :

- Transglutaminase II inhibitors
- gliadin-targeting antibodies
- and polymeric binders.

- However, high methodological RCTs and clinical data are needed.


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- Normal TTG does not exclude intermittent or low-level gluten ingestion .

- Accidental ingestion of gluten is often hard to assess. For this purpose, the detection of gluten peptides in urine and faeces has been developed

- Routine use of gluten detection devices in food or biospecimens among patients with CD not recommended .
- This technologies may not detect between clinically significant and trivial gluten exposure

The American Journal of Gastroentrology, 2022

Current guidelines for the management of celiac disease: A systematic review with comparative analysis : WJG

Poor GFD compliance is common , and mucosal damage can persist despite negative serology and the absence of symptoms

- Normal tTG-IgA levels do not predict full recovery of villous atrophy.
- BUT, persistently positive serology 12 mo after GFD is a strong indicator of gluten ingestion
- The inability of serology alone to predict mucosal healing leads to consider the repeating biopsies after GFD.

Treatment is also essential for evaluating possible complications.

- Metabolic complications of GFD and Osteoporosis should also be evaluated.
- follow-up schedules are based on the frequency of complications, risk of non-compliance.

- Better to repeat BX after 2 years of GFD to assess mucosal healing.
- Some guidelines suggest re BX only for persistent symptoms or serological abnormalities after 12 m of GFD
- Risk of a complicated CD is higher in patients >40 years of age at the time of diagnosis or those with a classical presentation and better to have re biopsy

- Oats are derived from a different tribe and do not contain pure gluten.

- Uncontaminated oats are safe for almost all patients with CD, but a small percentage of patients may be sensitive to some oat cultivars and should be monitored

Fallow up evaluations

- Dietary interview
- laboratory tests.

Evaluate micronutrients malabsorption, including CBC, iron status, folate, B12, Ca, phosphate, vitamin D

- should monitor associated autoimmune conditions

TSH and serum glucose and liver

ACG recommend:

vaccination to prevent pneumococcal disease in patients with CD (conditional recommendation, low quality of evidence).

Vaccination for all adults older than 65 years and smokers aged 19–64 years or adults with certain underlying conditions.

Alberto Rubio-Tapia,et al . Am J Gastroenterol 2023

BMD?

- According to some guidelines, BMD in every patient at the time of diagnosis and should be repeated after 3 years if abnormal, or 5 years if normal

- Other guidelines :BMD only in patients with high risk of osteoporosis or those older than 55 years.

