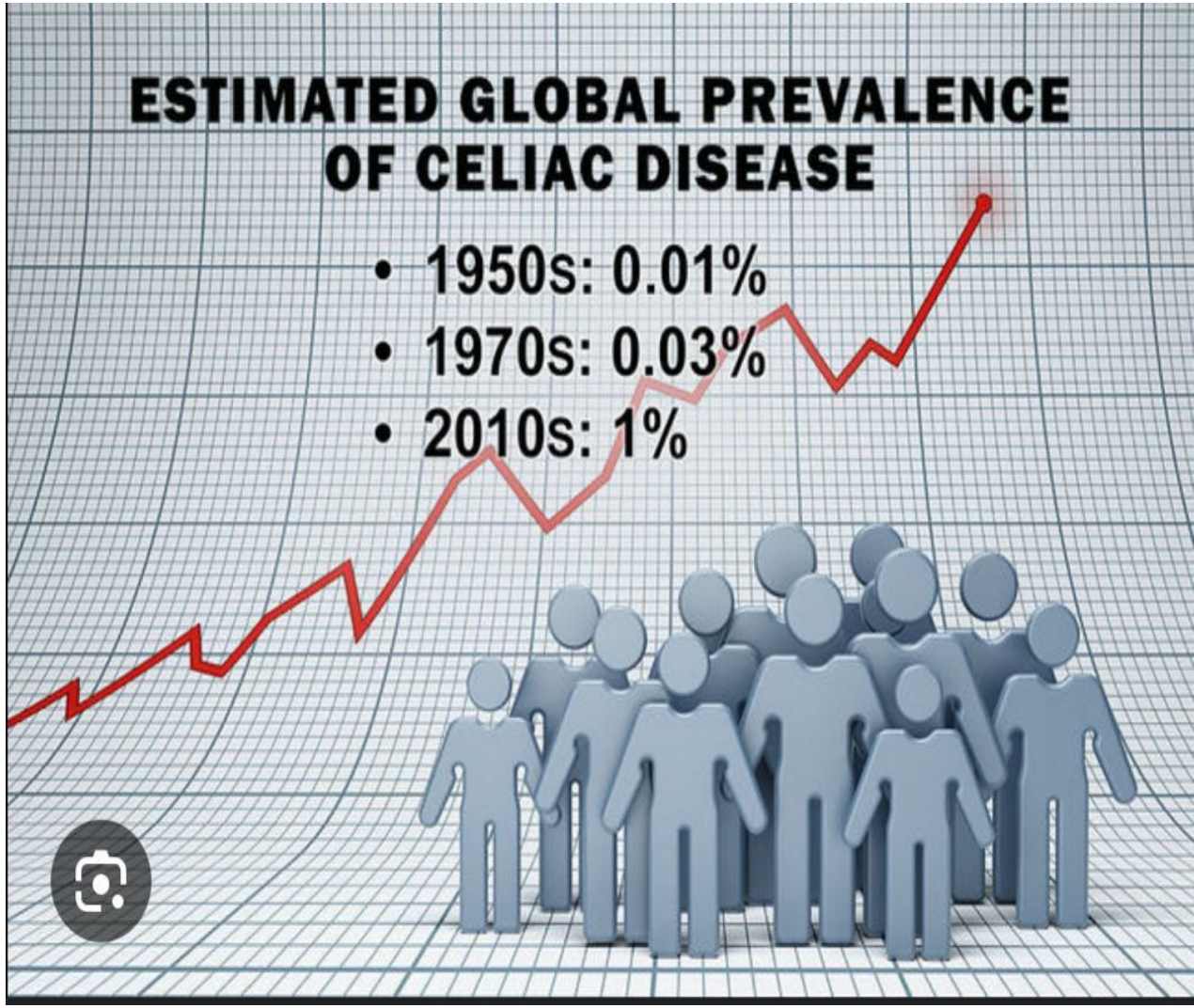
Celiac disease: physiopathology and management up date

Sarah al-amine M.D

28-11-2024

Celiac is a common disease

- Common,affecting 1% of population worldwide
- The prevalence of celiac disease has increased 6 or 5-fold since 1950
- increasing, with an average of 7.5% increase per year over the past several decade



Estimates

US Prevalence:

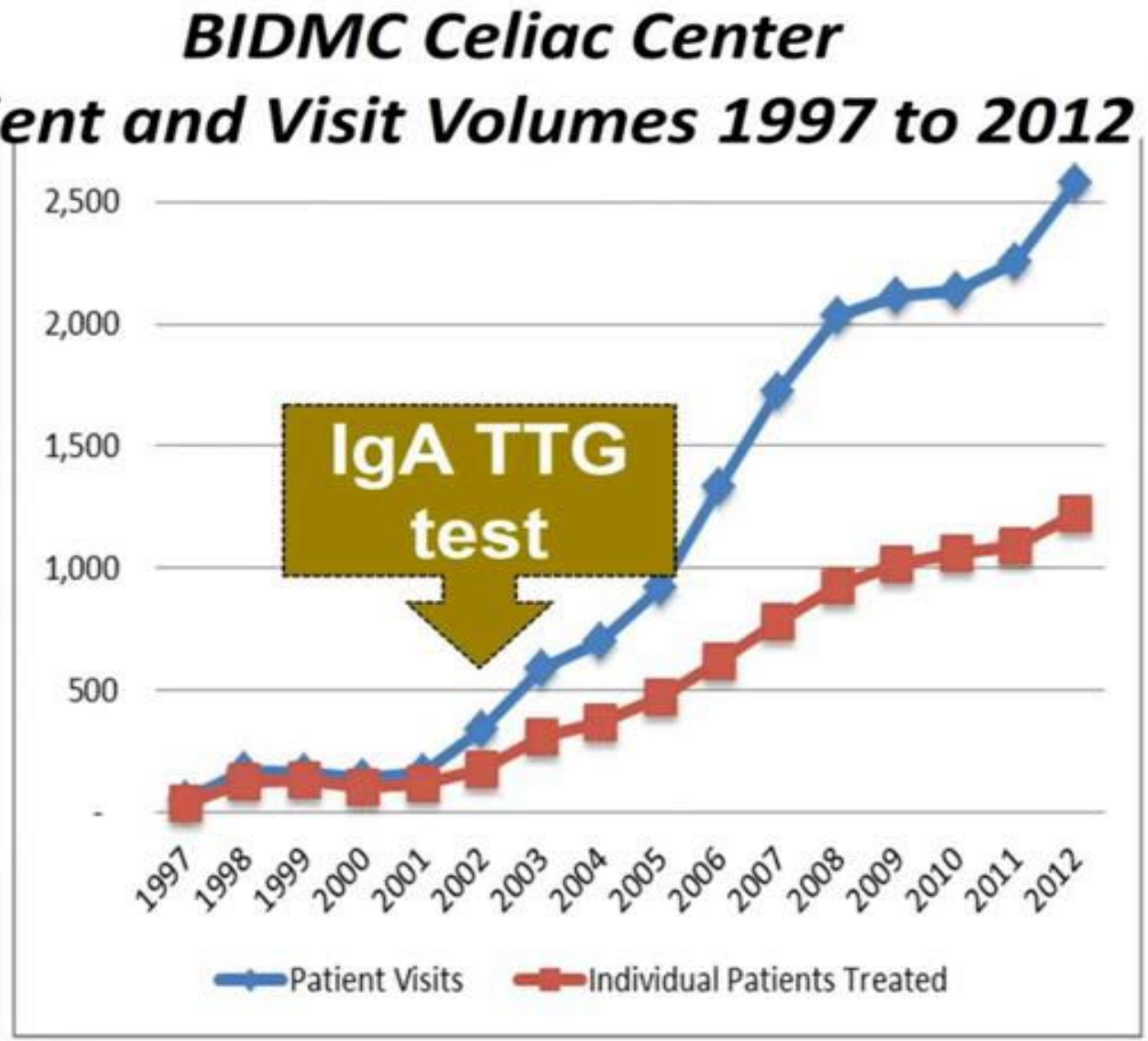
1995: 1:4,587 **(~0.02%)**

2021: 1:100 **(~1%)**

US Diagnosed cases

1994: **3%** of cases

2015: **15%** of cases



Talley, Am J Gastroenterol, 1994. Fasano, Arch Int Med. 2003. Rubio-Tapia A, Gastroenterol 2009.

Celiac disease: More common or just more commonly diagnosed?

Then:

9,133 healthy young adults at Warren Air Force Base

1950: Blood collected (1948 to 1954)

0.2% with CD (positive TTG)

Now:

12,768 gender-matched subjects from 2 more recent US cohorts

Circa 2000:
Similar years of birth (n = 5558)
Similar age at sampling (n = 7210)

0.9% with CD [x 4.5; P < .001].

Rubio-Tapia A et al. Gastroenterol 2009;137:88-93. Lohi S et al. Aliment Pharmacol Ther 2007;26:1217-25

Celiac disease treatment

- Gluten-Free Diet (GFD) is currently the only proven treatment for CD
- strict GFD is challenging

Research report

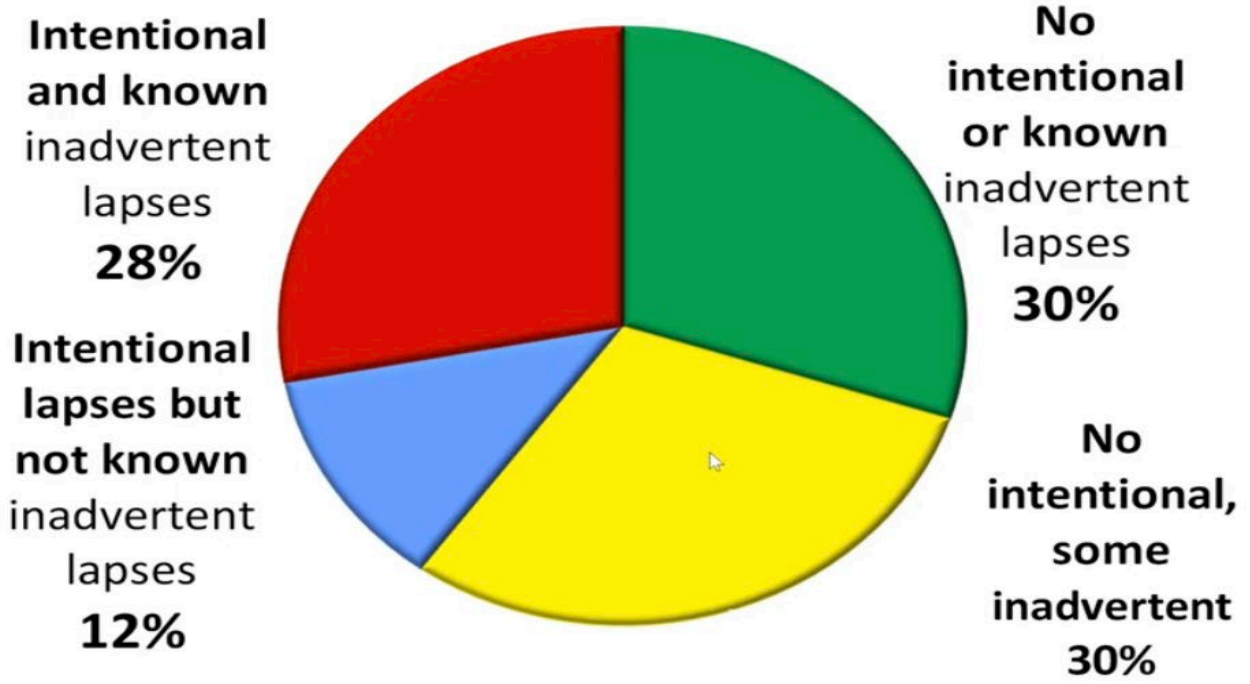
Intentional and inadvertent non-adherence in adult coeliac disease. A cross-sectional survey ☆

Nicola J. Hall [a,*], Gregory P. Rubin [a], Anne Charnock [b]

[a] Wolfson Research Institute for Health and Wellbeing, Durham University, School of Medicine, Pharmacy and Health, Queen's Campus, Stockton on Tees TS17 6BH, UK
[b] Faculty of Education and Society, Sunderland University, Priestman Building, Green Terrace, Sunderland SR1 3PZ, UK

Appetite 2013,1; 56–62

Most Celiac disease patients have gluten exposures on the GFD



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, 2(

- less than **40%** of CD patients achieve long-term adherence to a GFD
- up to **80%** of GFD-adherent patients might have inadvertent gluten

strict GFD is challenging

- **dietary regimens** are the least appealing medical strategies, the **lowest** rate of adherence the highest adherence rate is medication
- Gluten is the Latin word for "**glue**", and its viscoelastic
- processed **foods**, even in **unlikely foods** (such as yogurt and frozen fish) and **products** (such as toothpaste and lipstick).

Can hold air / water
Elasticity and extensibility properties from dough

http://grist.org/food/2011-11-10-gluten-why-all-the-fuss/
https://www.celiackidsconnection.org/gluten-2/

How Much Gluten Dose It Take?

a typical diet	**15–20 g/day**
induce mucosal atrophy	50 mg/day cutoff 1% of a slice of bread
gluten exposure	150 mg/day

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Limitation of GFD

- Many **(most)** suffer episodic **symptom** recurrences
- **~ 30% of** adults on strict GFD not achieve **histological recovery**
- **~10% non-responsive** to GFD
- **1 - 2%** refractory CD
- Increase risk of **obesity** offer feeding low fiber

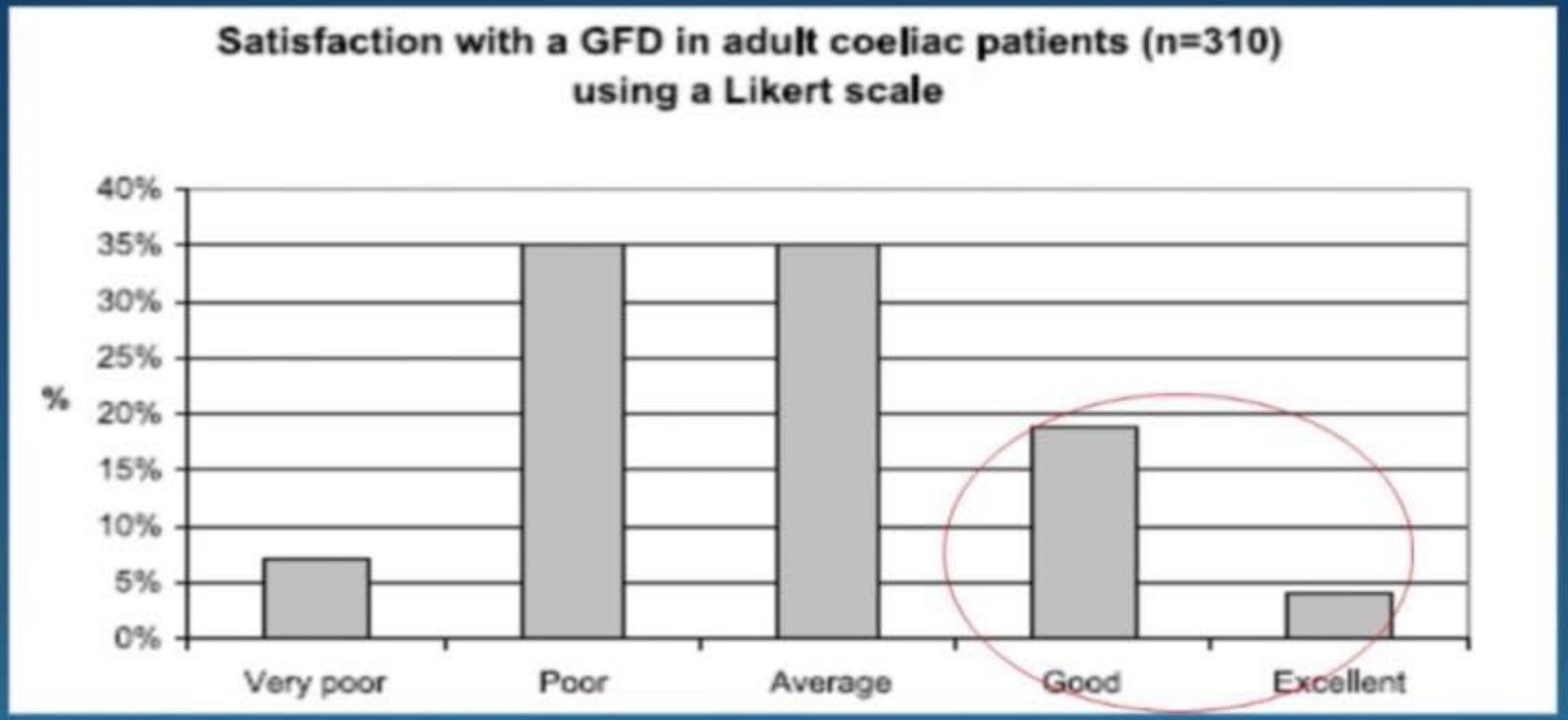
Rubio-Tapia et al. ACG Clinical Guidelines. Am J Gastroenterol.2013;108:656-76 O'Mahony et al. Aliment Pharm Thera 1996

Are Patients with Coeliac Disease Seeking Alternative Therapies to a Gluten-free Diet?

Imran Aziz, Kate E Evans, Vasiliki Papageorgiou, David S Sanders

Department of Gastroenterology, Royal Hallamshire Hospital, Sheffield, UK

J Gastrointestin Liver Dis
March 2011 Vol. 20 No 1, 27-31



WCOG@ACG2017
October 13-18
Orlando, Florida

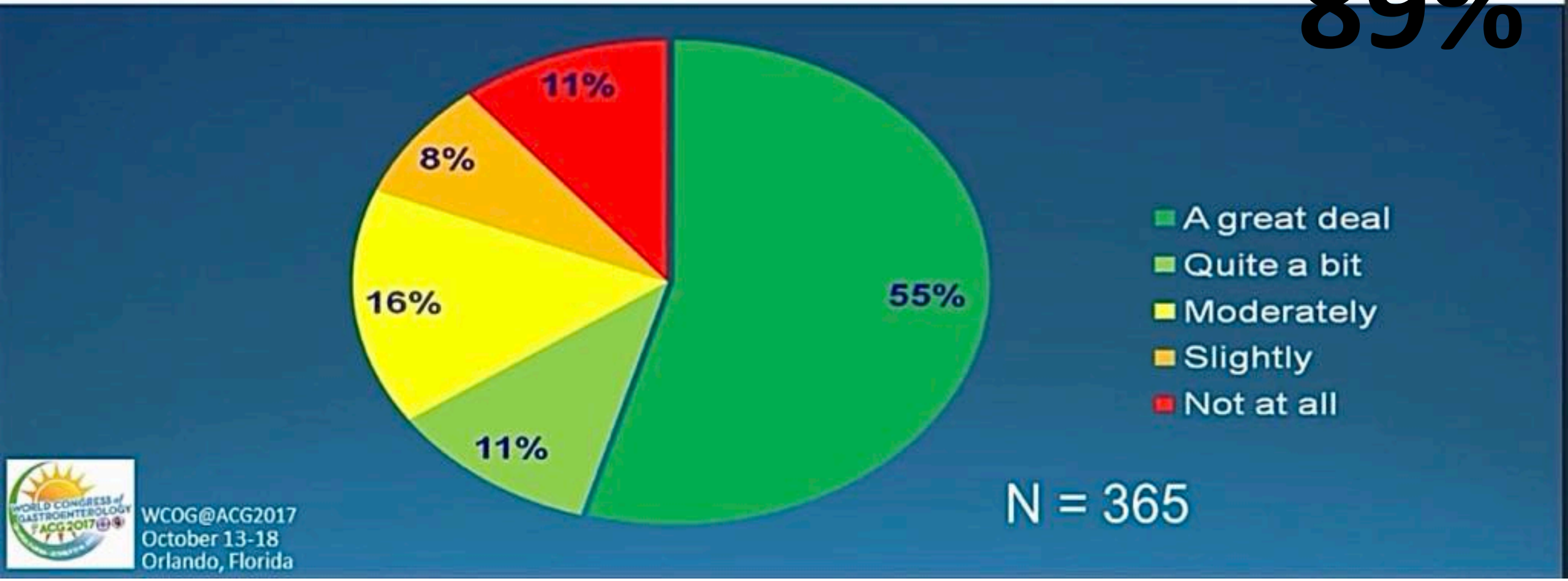
All subjects were interested in an alternative therapy

Ther Adv Gastroenterol
(2013) 6(5) 358–364
DOI: 10.1177/1756283X13492580

Interest in medical therapy for celiac disease

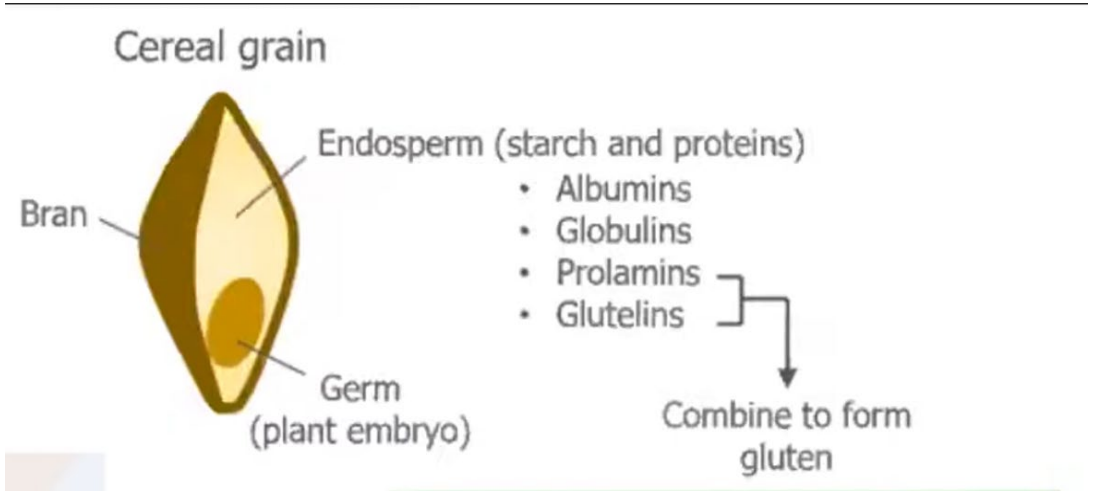
Christina A. Tennyson, Suzanne Simpson, Benjamin Lebwohl, Suzanne Lewis and Peter H. R. Green

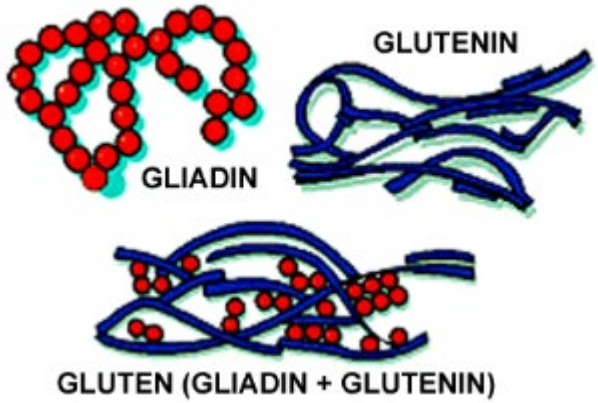
89%



physiopathology

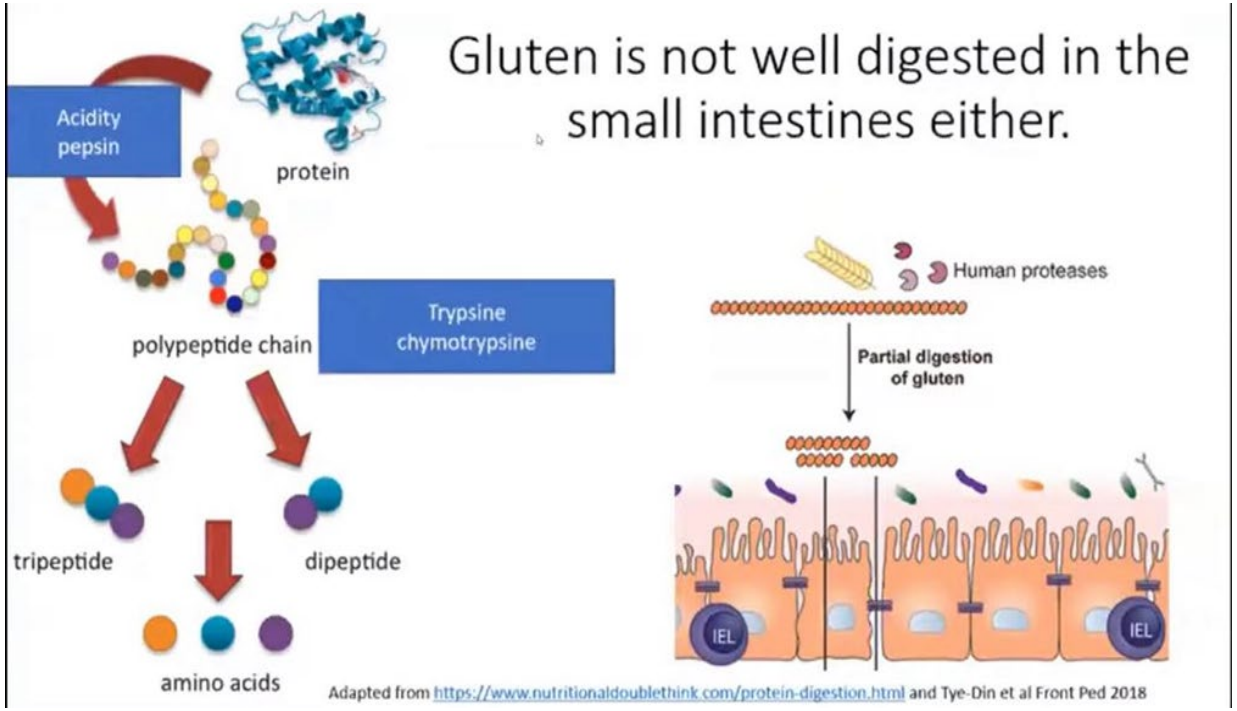
Gluten is the general term for a protein found in wheat, barley and rye



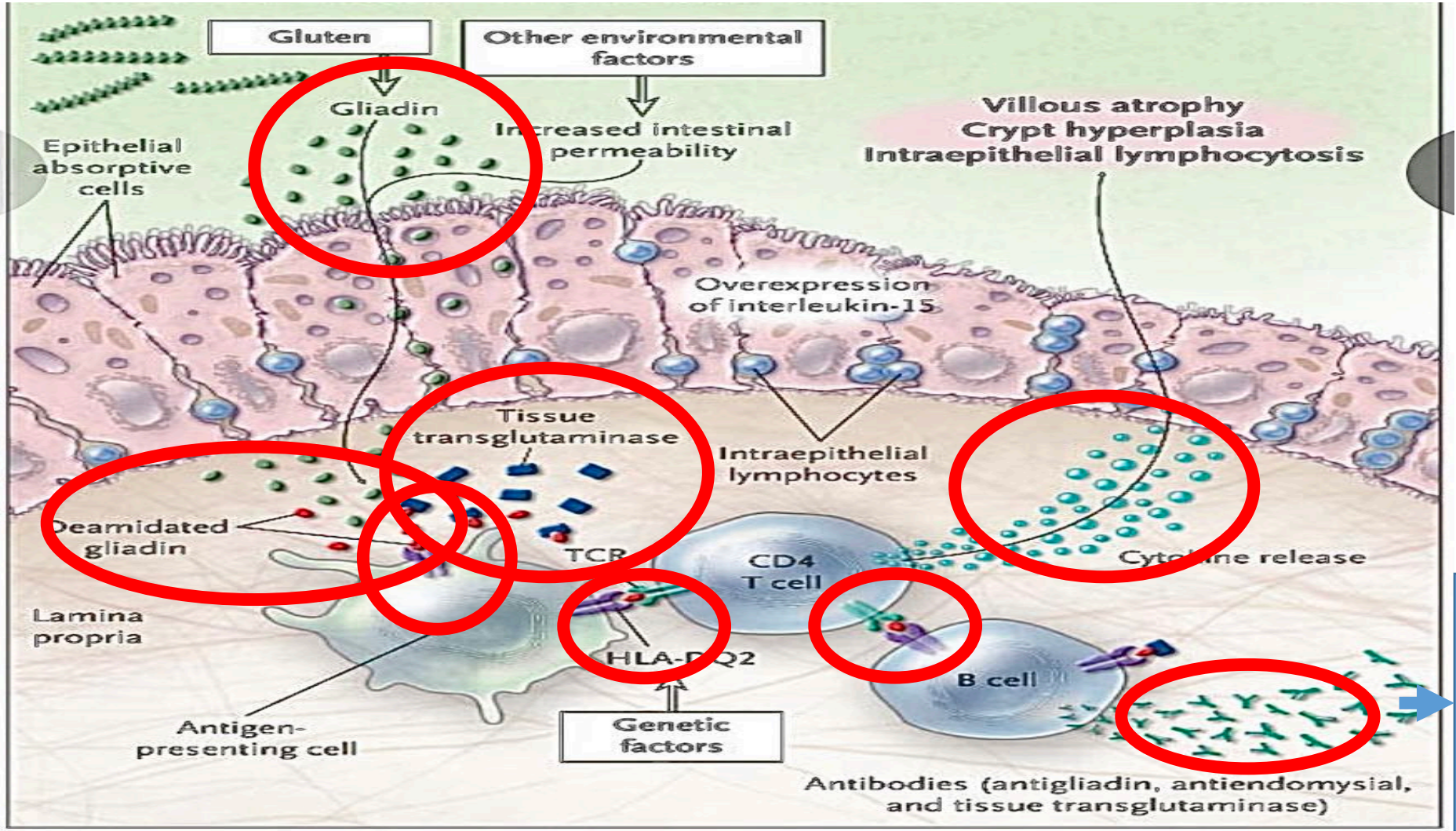


Gluten is not well digested in the small intestines

- high resistance to the action of human proteases in the intestinal lumen
- results in the production of peptides
  33 amino acids in length calld gliadin that are highly immunogenic



Physiopathology

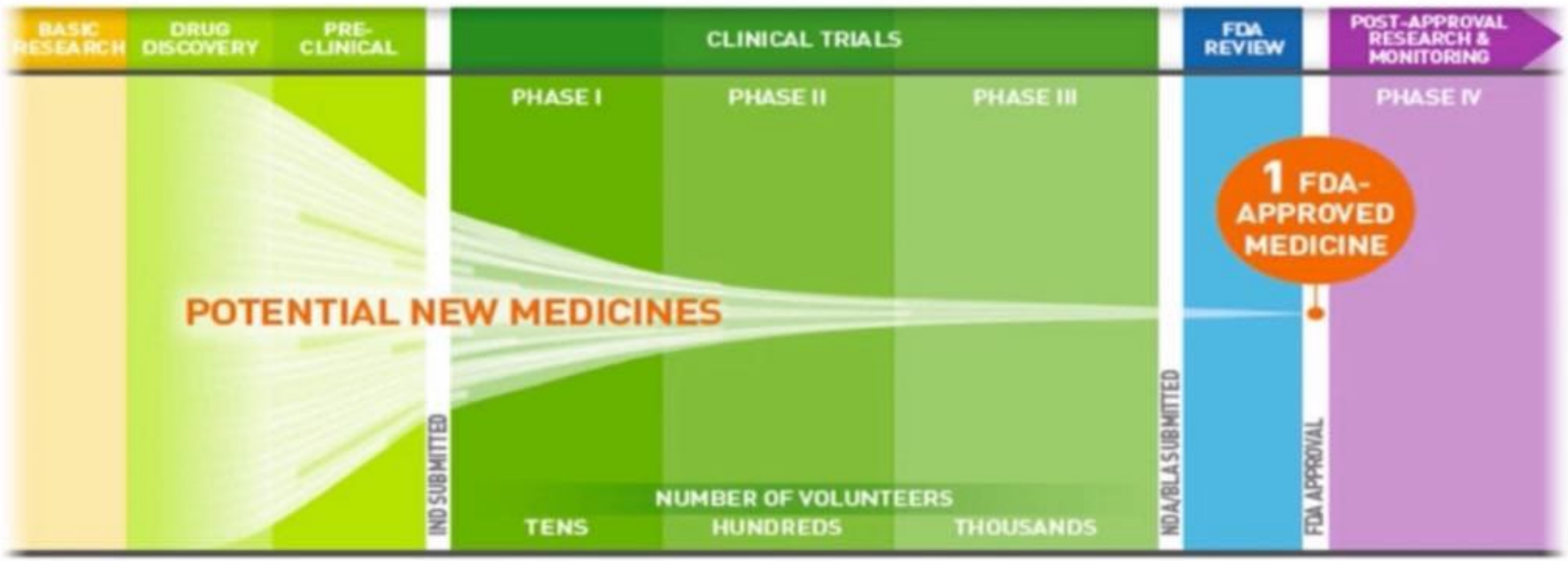


Anti gliadin
Anti deamidated gliadin (DGP)
Anti tTG
Anti endomysium
Anti actin

NEJM 2007

FIGURE 14: The Biopharmaceutical R&D Process

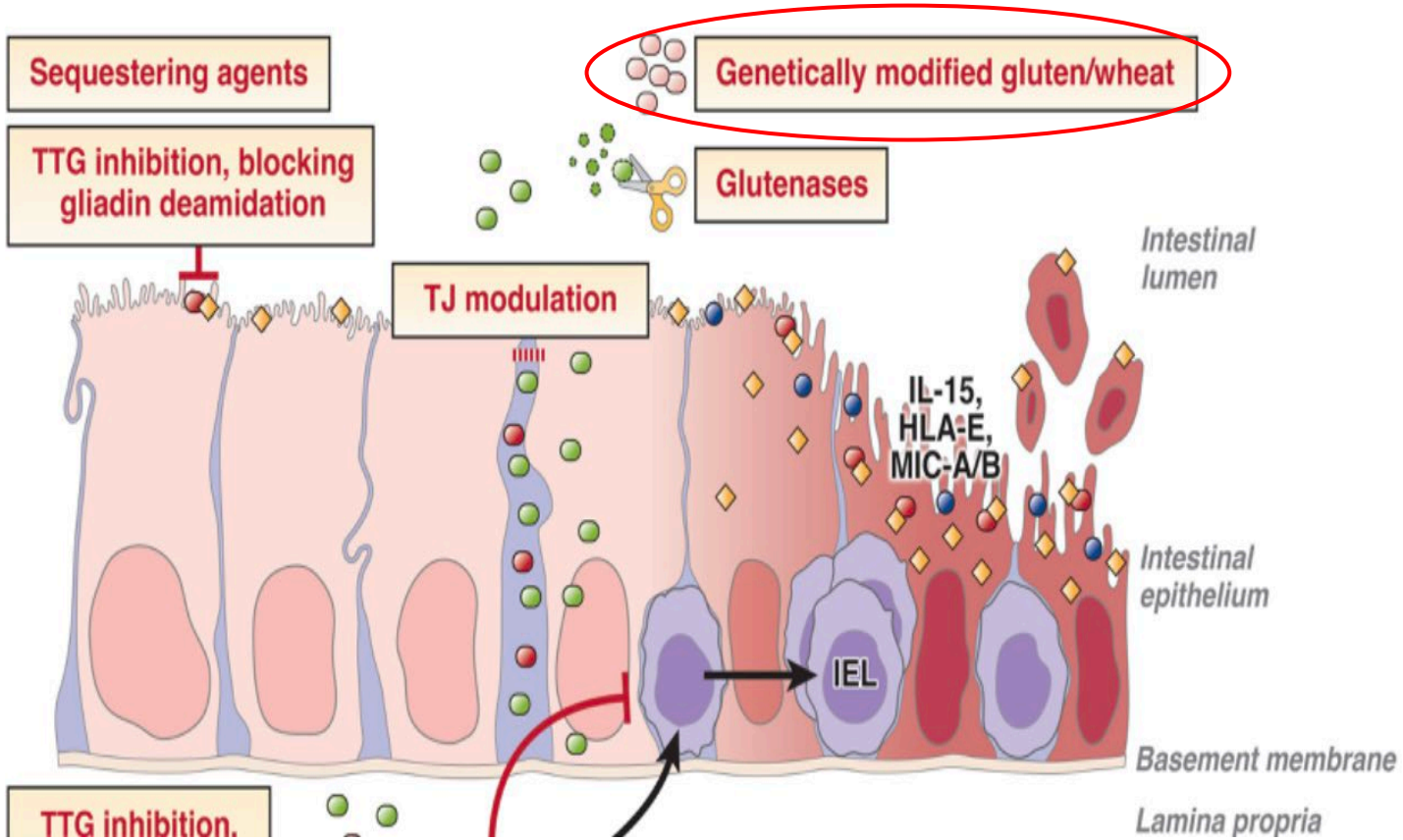
From drug discovery through FDA approval, developing a new medicine on average takes at least 10 years and costs $2.6 billion.* Less than 12% of the candidate medicines that make it into phase I clinical trials will be approved by the FDA.



Key: IND: Investigational New Drug Application, NDA: New Drug Application, BLA: Biologics License Application

Therapeutic Strategies

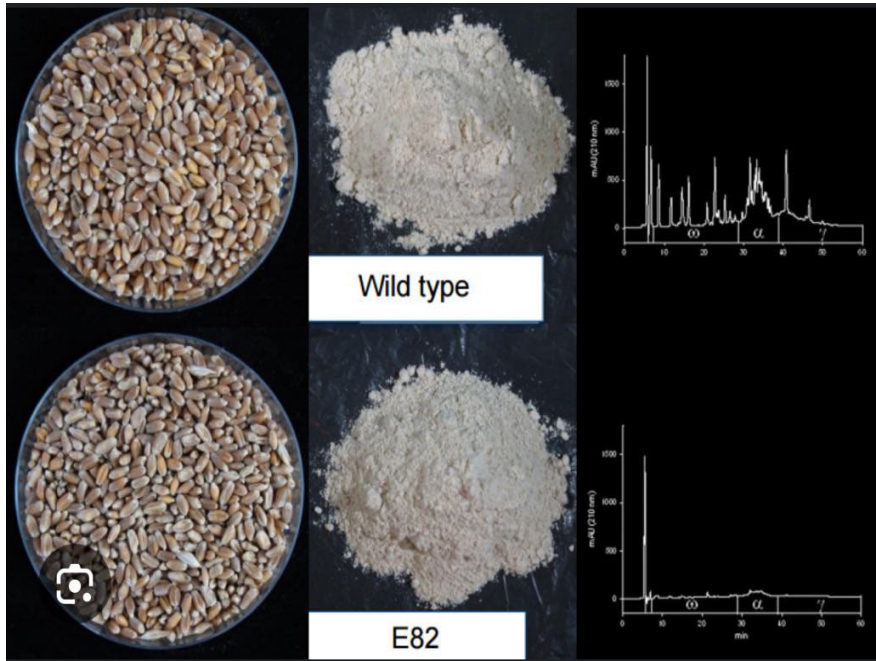
- Strategy 1 : reduction of Gluten load



1. removing gluten from the diet
2. Genetically modified gluten wheat

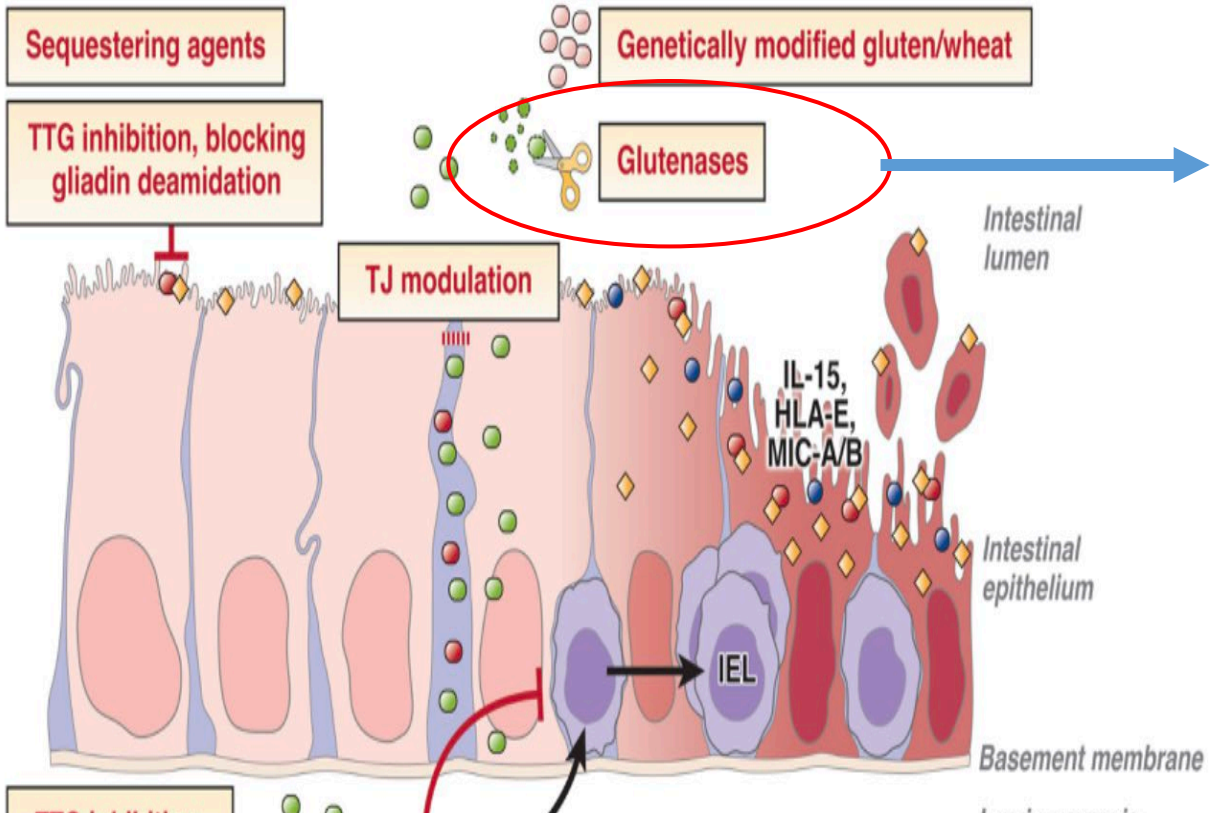
1-(E82 WHEAT)

- genetically engineer non-immunogenic wheat
- This is not an easy task
- silencing one gene would not be enough . Need to block for 100 genes
- E82 wheat line produced by RNAi technology that blocks relevant gliadin genes
- **pilot study** with:
  - 21 CD patients:
  - eating E82 wheat
  - ↓(INF-$^{\gamma}$)in peripheral blood
  - Very low level gluten immunogenic peptides (GIP) in stool



Strategy 1 : reduction of Gluten load

2-Enzyme therapy(Endopeptidases)



- *Latiglutenase*
- *TAK062; Takeda*

- human proteases are ineffective at degrading gluten proteins.
- could be achieved by exogenous endopeptidases
- digest, the gluten proteins into small non-immunogenic peptides before they reach the duodenum.
- stable in the low pH gastric environment

Latiglutenas

- an orally administered mixture of two gluten proteases

Agent	Study	Trial Phase	Population	Treatment	Duration	Main Results (vs. Placebo)
			Endopeptidases			
Latiglutenase	Tye-Din, 2010 [59]	1	20 CD patients on a gluten challenge (16 g/day)	800 mg/day vs. placebo	3 days	• ↓ INF-γ secretion by gluten-specific T cells in peripheral blood
	Lahdeaho, 2014 [60]	2a	41 CD patients on a gluten challenge (2 g/day)	900 mg/day vs. placebo	6 weeks	• Prevented mucosal deterioration (no ↓ Vh:Cd or ↑ IEL) • No improvement in symptoms
	Murray, 2017 [61]; Syage, 2017 [62]	2b	494 CD patients with moderate or severe symptoms on a GFD ≥ 1 year	100 mg, 300 mg, 450 mg, 600 mg, or 900 mg/day vs. placebo	12 or 24 weeks	• No ≠ in Vh:Cd or ↑ IEL • No ≠ in serology • Improvement in the symptoms of seropositive patients with ≥600 mg/day
	Murray, 2022 [63]	2b	43 CD patients on a gluten challenge (2 g/day)	1200 mg/day vs. placebo	6 weeks	• Prevented mucosal deterioration (lower ↓ Vh:Cd) • Tendency to decrease symptoms
	NCT 04243551	2b	120 symptomatic CD patients undergoing periodic gluten exposure	vs. placebo	6 weeks	Ongoing Estimated completion May 2023

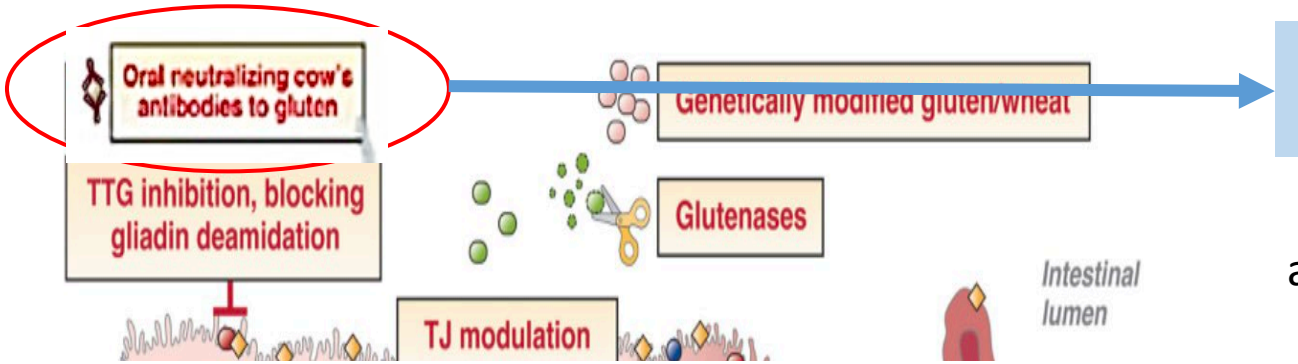
TAK-62

- glutenase effective in vitr,
- capable of degrading 97%-99% of gluten in gastric 20-65 min after guten ingestion
- well tolerated dose 900 mg

TAK-062	Pultz, 2021 [65]	1	CD in GFD and healthy subjects after a gluten meal (3–9 g)	100–900 mg	6 weeks	• Well tolerated

Strategy 1 : reduction of Gluten load

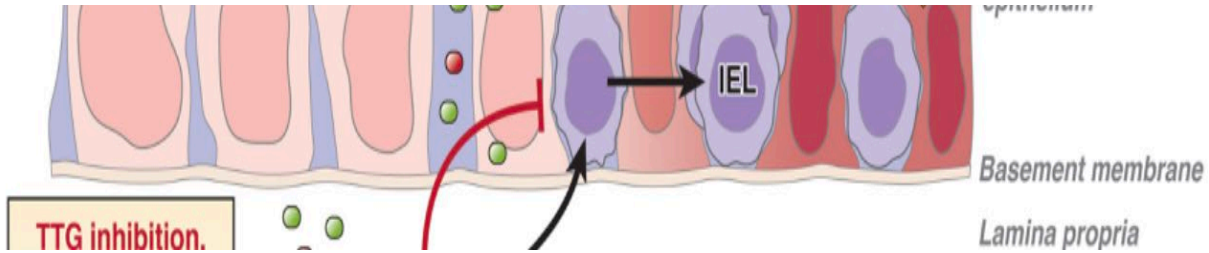
- 3- Gluten sequestration antibodies to gluten



- AGY

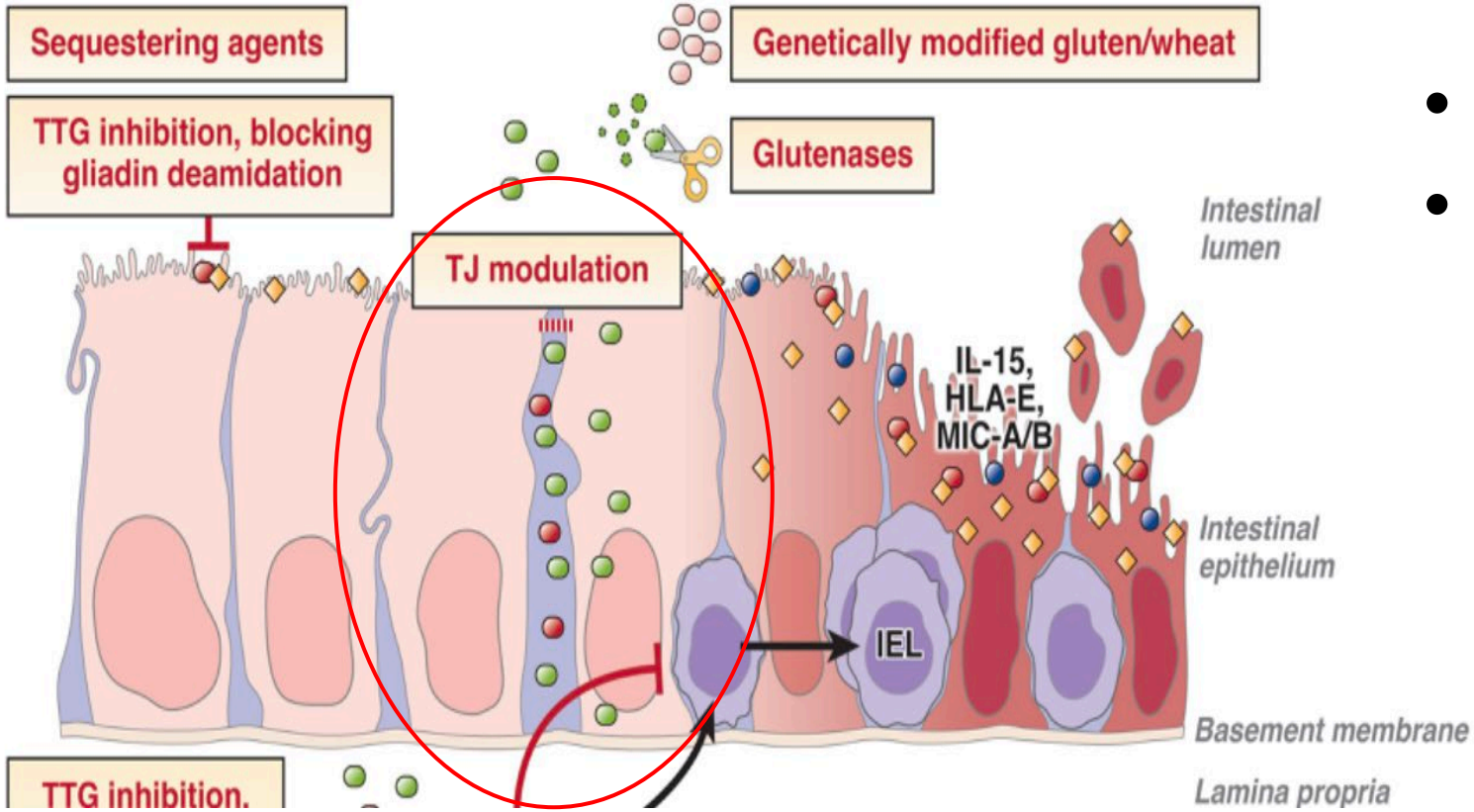
an oral egg yolk anti-gliadin polyclonal antibody

AGY	Sample, 2017 [66]	1	10 CD patients on a GFD	1000 mg bid	4 weeks	• ↓ symptoms • ↓ serology • ↓ LMER
	NCT 03707730	2	Symptomatic CD patients on a GFD	Before meals vs. placebo	14 weeks	Ongoing Completion December 2022

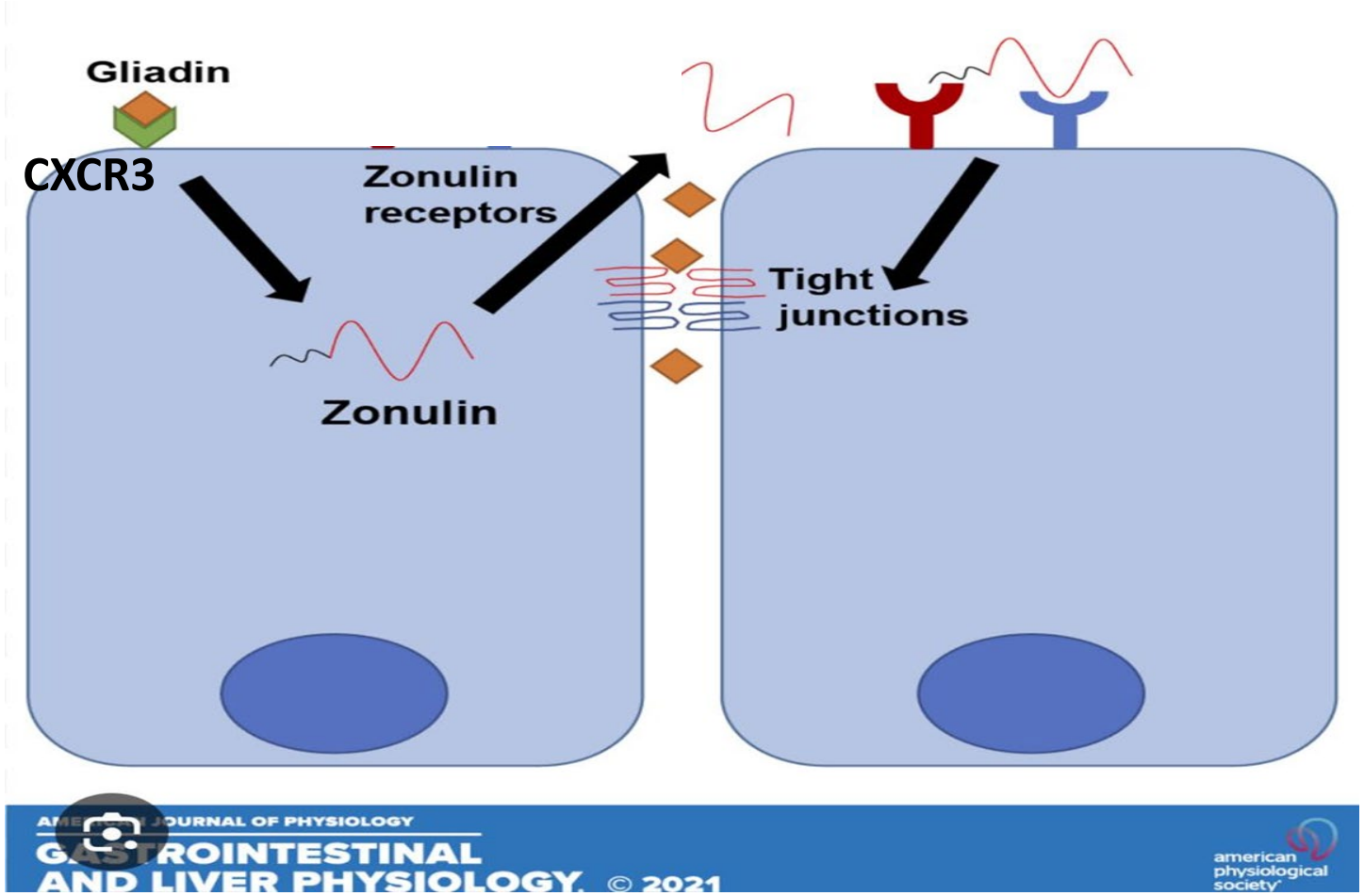


Strategy 1 : reduction of Gluten load

- Tight junction modulation



- CD loosn the tight junctio
- Increase intestinal permeability



Larazotide

1. blocking its receptor
2. inhibitorof zonulin
3. ↓permeability

Larazotide

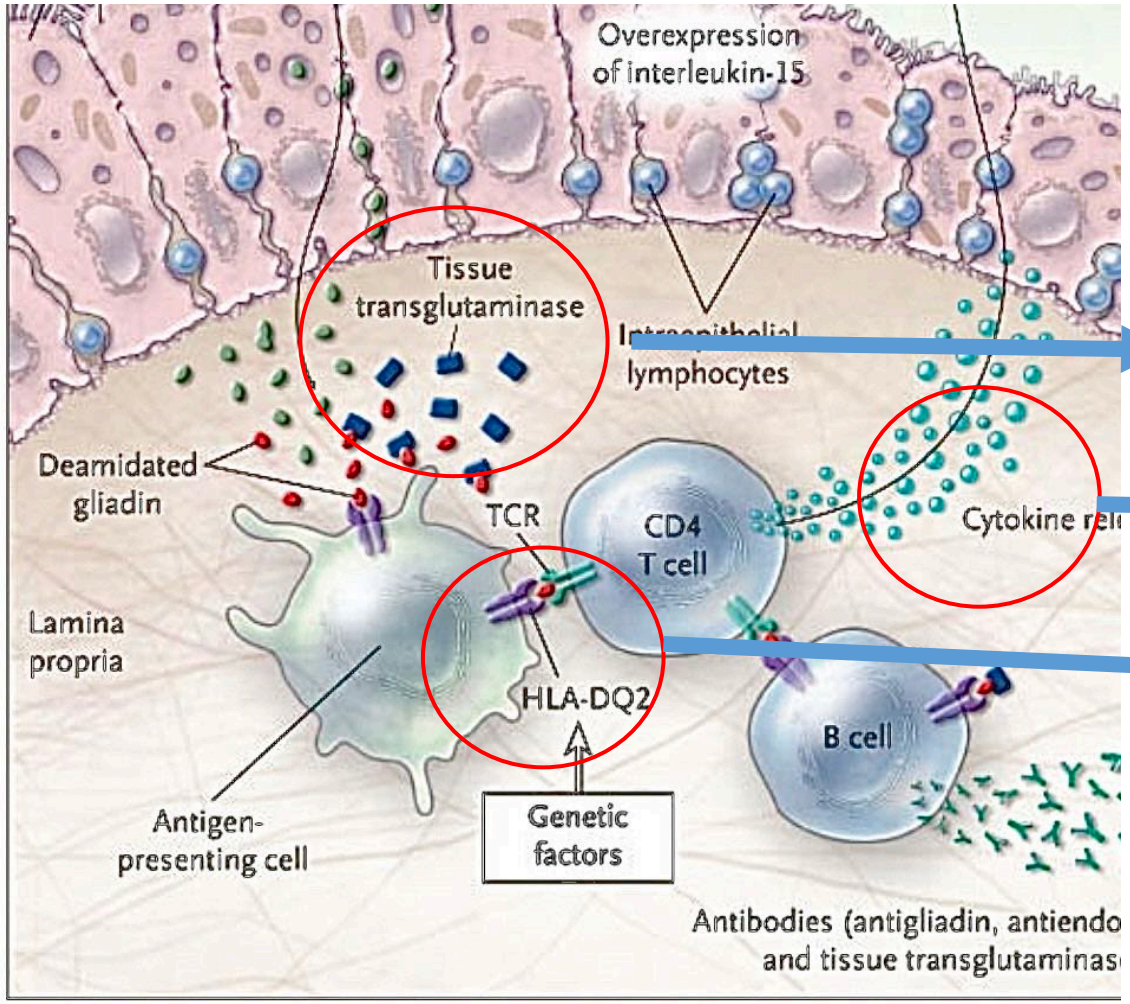
- Phase 3 randomized, double-blinded, placebo-controlled study of 525 patients

6/21/2022

9 Meters Discontinues Phase 3 Clinical Trial for Potential Celiac Disease Drug Larazotide

An analysis by an independent statistician of the ongoing Phase 3 trial for Larazotide, referred to as CedLara, has co
that a substantial number of new patients would have to be added to the existing trial in order to get scientifically r
results. 9 Meters determined that the additional number of patients needed was too large to support the continuat
trial. The Celiac Disease Foundation was proud to partner with 9 Meters to recruit patients for this trial.

Strategy 2: : Immune Modulation



Blocking cytokine:

Anti–IL-15 (PRN-015)

anti a4b7 (Vedolizumab-PTG-100)

anti-CCR9(Vercinon)

Tofacitinib

anti-TNF-a

Anti-Ox40L (amlitelimab; Sanofi)

Strategy 2: : Immune Modulation

- *ZED1227 Transglutaminase Inhibition :*
  - Blocking, TG-2 deamidation for gliadin by converts glutamine residues in glutamic acid
  - ↓permeability :TG-2 enzyme also induces degradation promotes transcellular intestinal permeability to gluten
  - phase 2 :
    - improved symptoms –gluten challenge 3g per day No in Vh:Cd or IEL
    - well tolerated, (a cutaneous rash in only 8% of patients on 100 mg) .
- DONQ52 : anti(DQ2.5-glia-a2)
  - HLA-DQ2.5–positive
  - Preclinical
- Anti cytokine : side effect ++ - RCD

Agent	Study	Trial Phase	Population	Treatment	Duration	Main Results (vs. Placebo)
Lymphocyte trafficking						
PTG-100 (anti-α4β7)	NCT 04524221	1b	30 CD patients on a gluten challenge	600 mg bid vs. placebo	42 days	Completed in April 2022 No data published so far
Vedolizumab (anti-α4β7)	NCT 02929316	2	CD patients on a gluten challenge	300 mg vs. placebo	6 weeks	Terminated in 2018 due to lack of enrollment
Vercinon (anti-CCR9)	NCT 00540657	2	30 CD patients on a gluten challenge	250 mg bid vs. placebo	13 weeks	Completed in 2008 No data published so far
IL-15 targeting						
PRN-015 or AMG714 (anti-IL-15)	Lähdeaho, 2019 [102]	2a	64 CD patients on a gluten challenge (2–4 g/day)	150 mg, 300 mg/day vs. placebo	12 weeks	• ↓ symptoms (diarrhea) • ↓ IEL at 300 mg • No ≠ in serology or Vh:Cd
	Cellier, 2019 [103]	2a	Type II RCD	8 mg/kg 2×/week vs. placebo	12 weeks	• ↓ symptoms (diarrhea) • No ≠ in IEL, aberrant IEL, or Vh:Cd • Adverse events: 26% vs. 11%
	NCT 04424927	2b	220 CD patients non-responsive to a GFD	3 ≠ arms vs. placebo	28 weeks	Ongoing Completion December 2023
Hu-Mik-β1 (anti-IL15Rβ1)	NCT 01893775	1	5 RCD patients	Every 3 weeks	9 weeks	Completed in December 2019 No data published so far
Tofecitinib (pan-JAK inhibitor)	Eudra CT: 2018-001678-10	2	Type II RCD (open-label) patients	10 mg bid	12 weeks	Ongoing

Strategy 3: immune Tolerance

- Re-educate the immune system to not reacts to the antigen

1- NexVax2 vaccine
2-TAK-101
3-KAN -101

THE LANCET
Gastroenterology & Hepatology

ancet.com/gastrohep Vol 2 July 2017

Epitope-specific immun… 4-positive
T cells in coeliac disease: tw… ouble-blind,
placebo-controlled phase 1 s…

Gautam Goel, Tim King, A James Daveson, Jane M Andrews, … F Brown, Ronald Fogel,
Charles F Barish, Roger Epstein, Timothy P Kinney, Philip … ela, Alina Popp, John Sidney,
Markku Mäki, Kaela E Goldstein, Patrick H Griffin, Suy… amnik J Xavier, Ludvig M Sollid,
Bana Jabri, Robert P Anderson

In this phase I stu…
Tolerable doses determined
Modified immune response to oral gluten
No deterioration in duodenal histology

=#

- Phase 2 : Terminated 2019 for futility no different vs placebo

(The intradermal administration may have hit the wrong target, being uptaken by APCs in the skin rather than the spleen and liver)

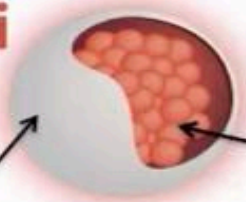
TAK-101

GLUTEN TOLERANCE ACHIEVED WITH IMMUNE MODIFYING PARTICLES

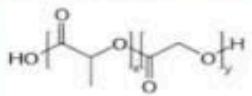
Tolerogenic Immune-Modifying Particles for Celiac (COUR-NP-GLI)

- Novel surface properties for targeted antigen delivery/immune modulation
- Antigen load ~ 2.9ug protein/mg polymer
- Antigen fully encapsulated for safety

TAK-101 + TIMP-Gli
Gluten in a Pocket

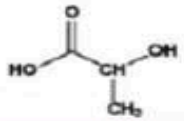


The Particle
PLGA with proprietary surface modifications

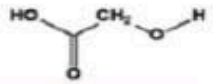


PLGA is biodegradable

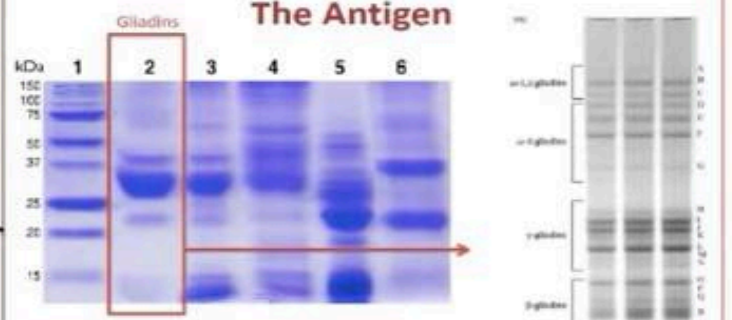
Lactic Acid



Glycolic Acid



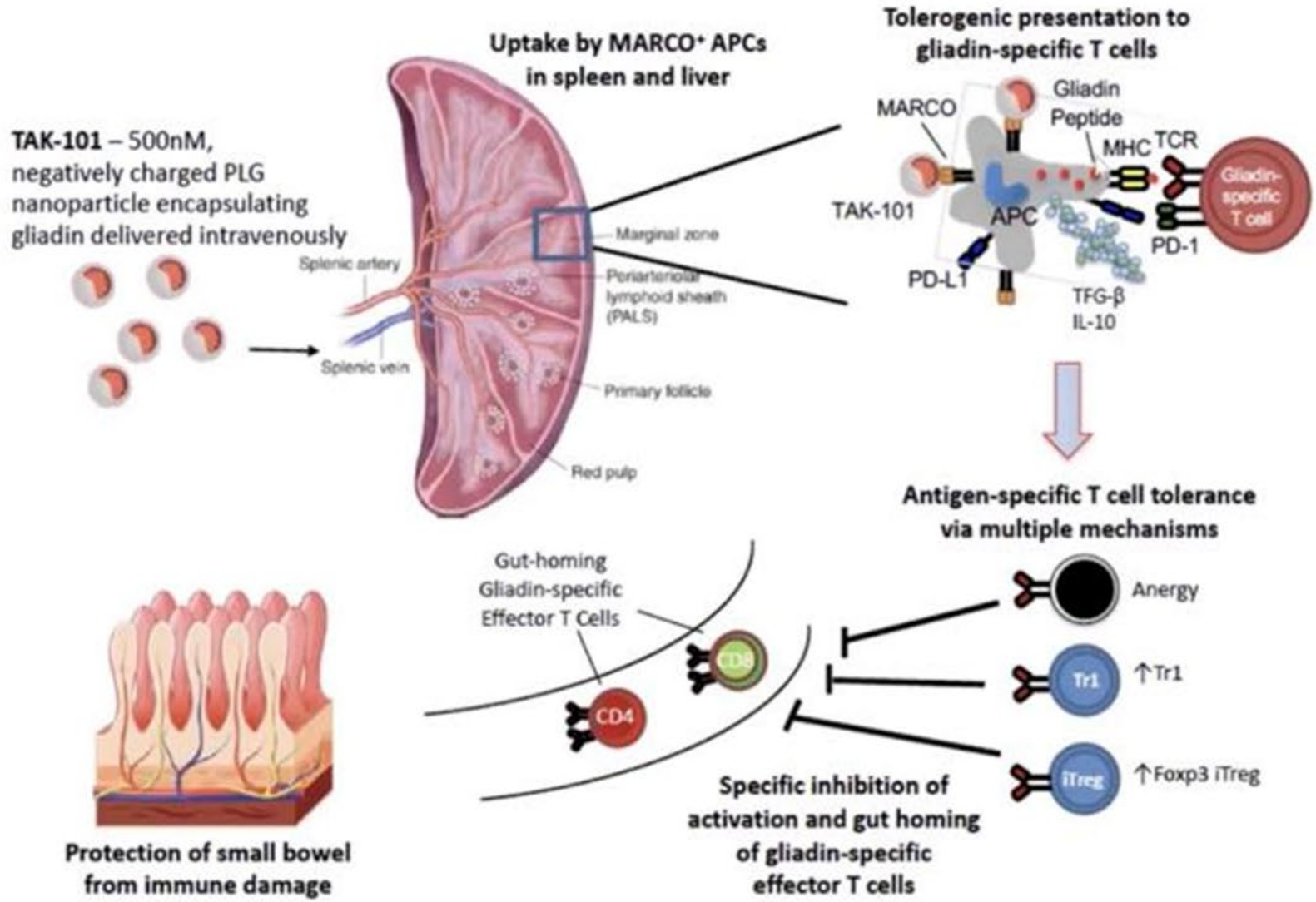
The Antigen



Particle (administered IV) is taken up via apoptotic pathway and trafficked to the spleen and processed by APCs.

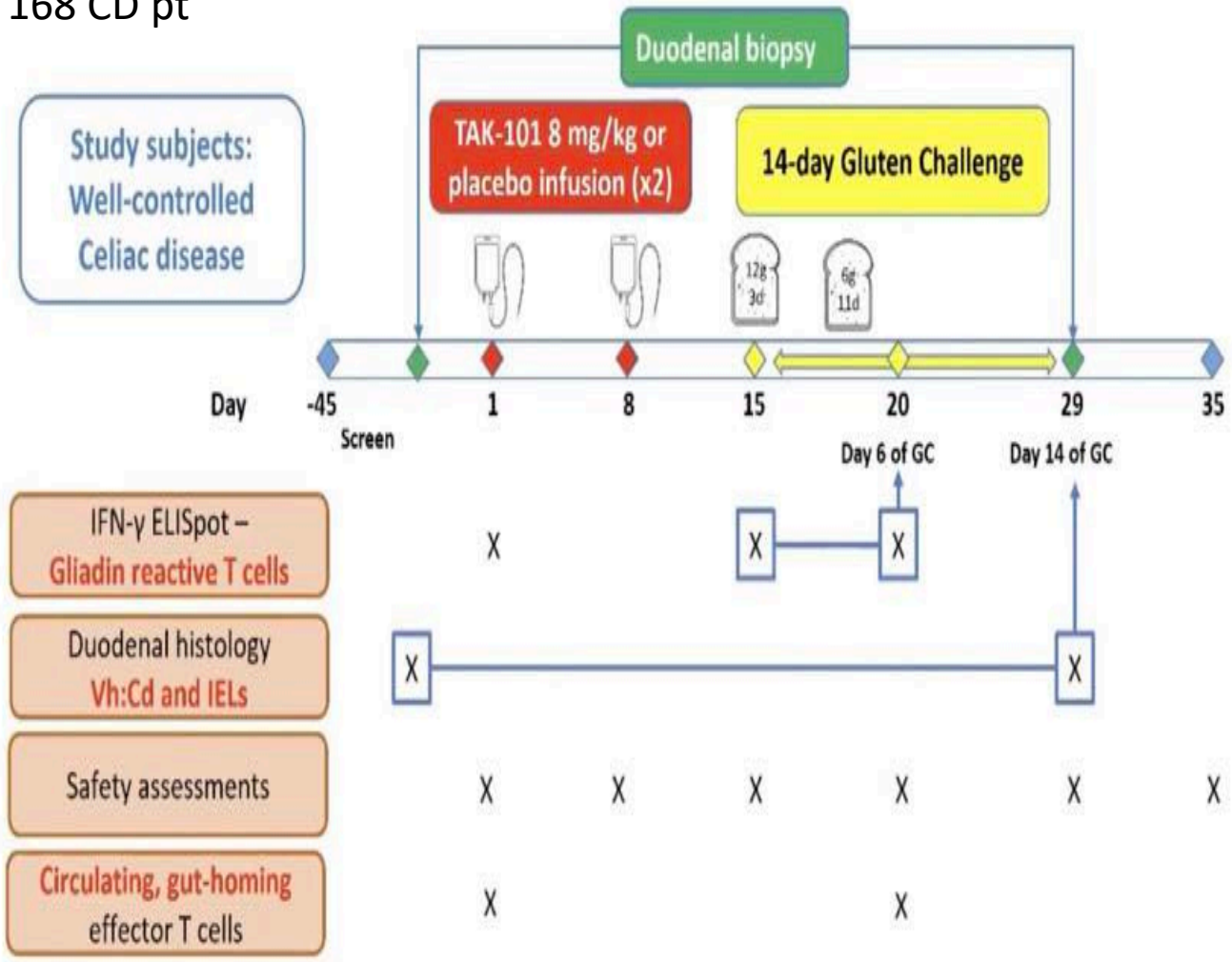
Getts DR et al. Nat Biotech 2012, 30:1217-24; Getts DR et al. Trends Immunol 2015, in press

TAK-101 Induces Tolerance to Gluten in CeD: MoA

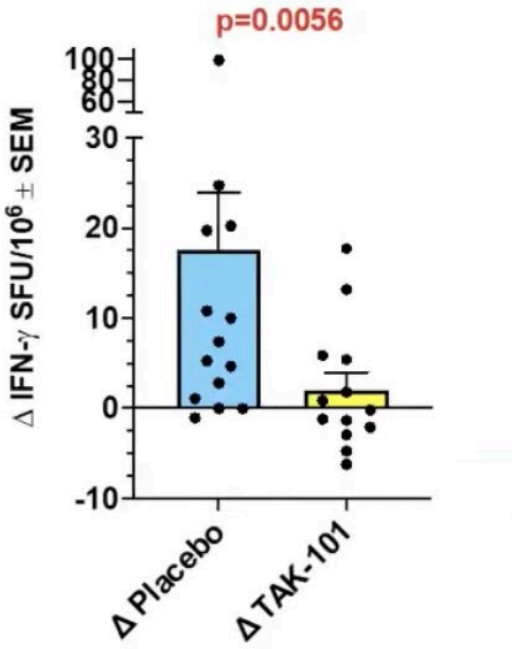


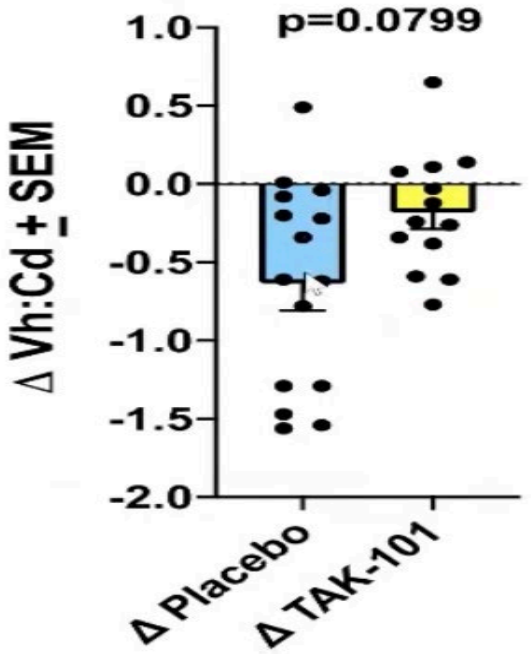
Phase 2a TAK-101 Proof-of-Concept study schematic

168 CD pt



CeD, celiac disease; ELISpot, enzyme-linked immunospot; GC, Gluten Challenge; IEL, intraepithelial lymphocytes; IFN, interferon; PBMC, peripheral blood mononuclear cell; Vh:Cd, villus height to crypt depth ratio





TAK -101 was safe and well tolerated: AE results of Phase 2a study

- No serious adverse events (SAEs)
- No clinically significant changes in:
  - vital signs,
  - routine clinical laboratory results
  - liver function tests (LFTs)
  - serum cytokines/chemokines
  - T cell proliferation
- Complement levels transiently raised in all patients, not associated with adverse events (AEs)
- Most AEs were mild and transient

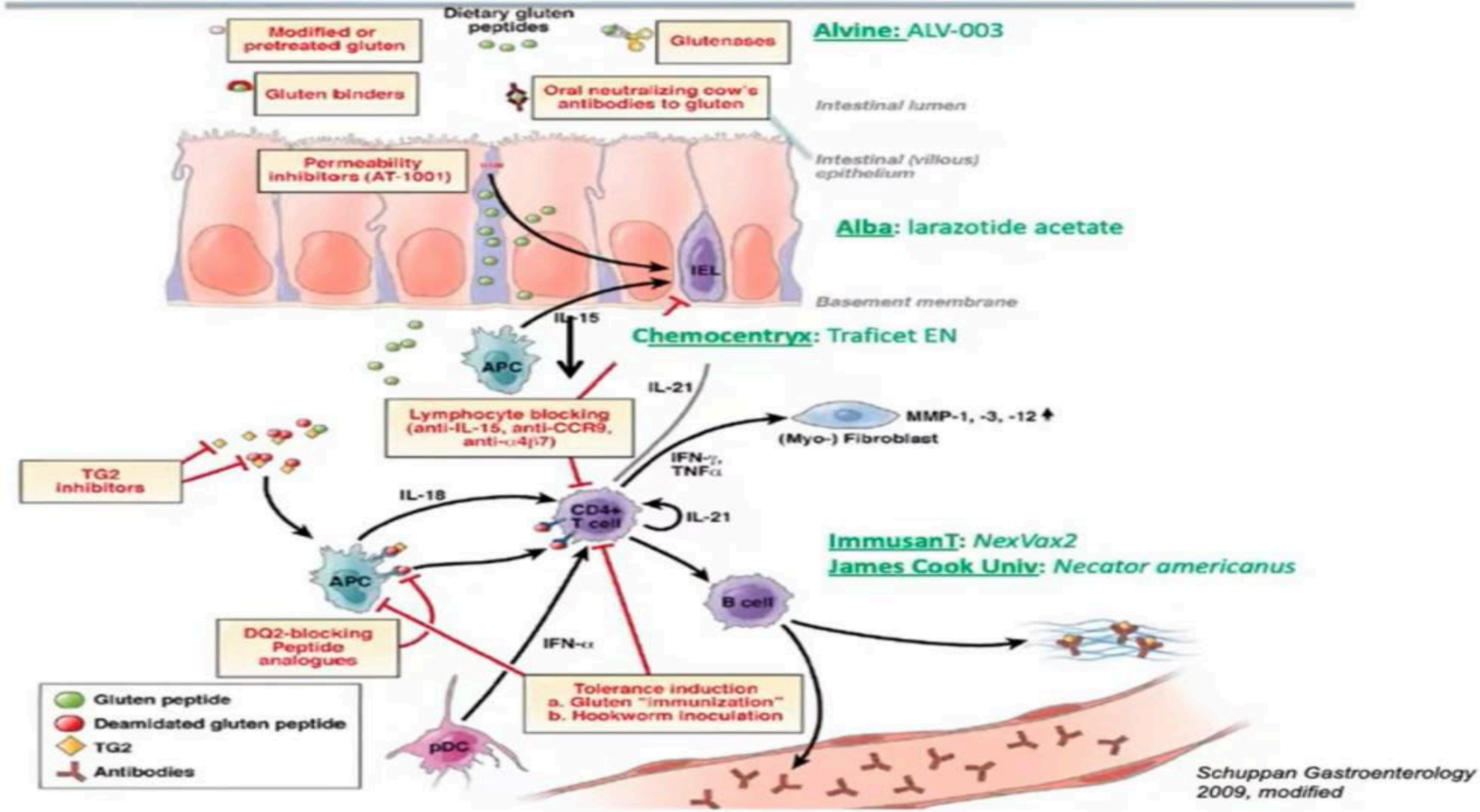
Phase 2a		
	CNP-101	Placebo
AE		
Nausea	81%	72%
Abdomen distention	56%	61%
Diarrhea	50%	50%
Headache	44%	17%
Abdominal pain	38%	28%
Vomiting	31%	33%
Fatigue	33%	50%
Back pain	31%	0%

AE, adverse event; CNP, Cour Nanoparticle Platform; LFT, liver function test; SAE, serious adverse event

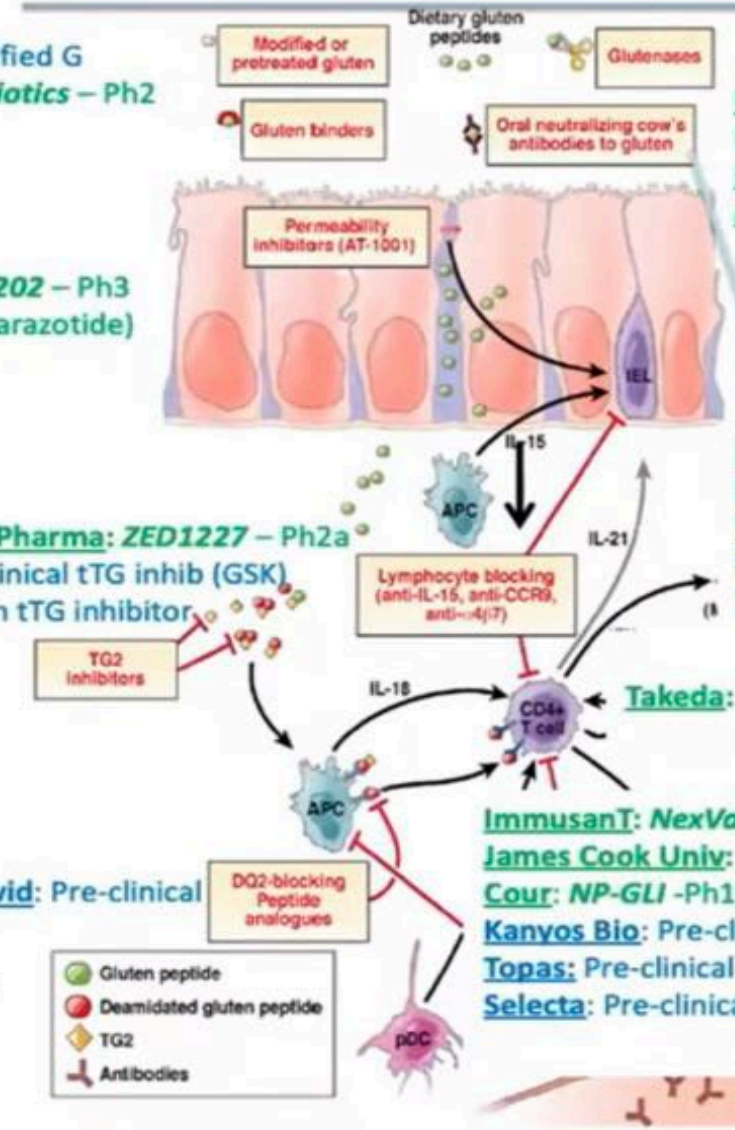
Take home messages

- The only proven treatment for CD is GFD
- **Latiglutenas:** mix of tow glutenase . You cant replace the GFD it help the diet . Strong contender to be a standard soon
- **Larazotide :** tight junctions -decreasing intestinal permeability- discontued for financial reasons
- **ZED1227:** blocking TG-2
- **TAK-101:** immune Tolerance

Experimental Non-Dietary Therapies For Celiac Disease (2010)



Experimental Non-Dietary Therapies For Celiac Disease (05/2021)



Universities: Modified G
Probiotics – Ph2

Innovate: – ***INN-202*** – Ph3
(formerly Alba's larazotide)

Zedira/Falk Pharma: ***ZED1227*** – Ph2a
Sitari: Pre-clinical tTG inhib (GSK)
UCB: Pre-clin tTG inhibitor

Provid: Pre-clinical

Schuppan Gastroenterology 2009, modified

ImmunogenX: ***Latiglutenase/IMGX-003***
(formerly Alvine's ALV-003)- Ph2b
PvP Biologics: ***KumaMax*** – Ph1 (Takeda)
Allergan: ***Viokase/pancrelipase*** – Ph2a

IGY Life Sciences: ***IgY*** – Ph1/2

Provention Bio: ***PRV-015*** (a.k.a. AMG 714) –Ph2b (Amgen)
Mayo Clinic/NCI: ***HuMikb1*** – Ph2a
Calypso: ***CALY 002***–Pre-clinical (Merck KGa)
Bioniz: ***BNZ-2*** – Pre-clinical (Takeda)
TEVA: ***04H04*** - Preclinical

Takeda: ***Vedolizumab/ENTYVIO*** – Ph1b

ImmusanT: ***NexVax2*** – Ph2a
James Cook Univ: ***Hookworm NainCeD-3*** – P1b
Cour: ***NP-GLI*** -Ph1b –(Takeda)
Kanyos Bio: Pre-clinical (Astellas/Anokion/Celgene)
Topas: Pre-clinical (Lilly)
Selecta: Pre-clinical

The hope for finding a cure may soon become reality

Thank you