Celiac Disease: The Future

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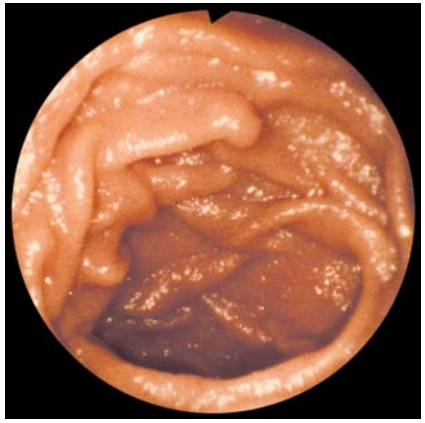
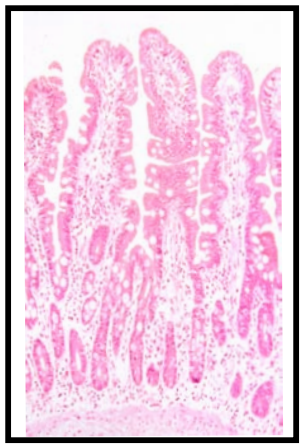
University of Maryland School of Medicine

Normal small bowel

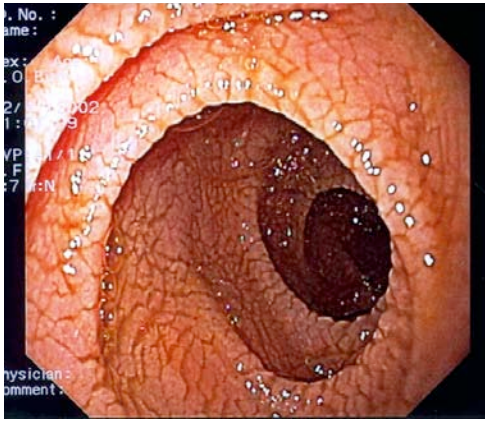
Celiac disease

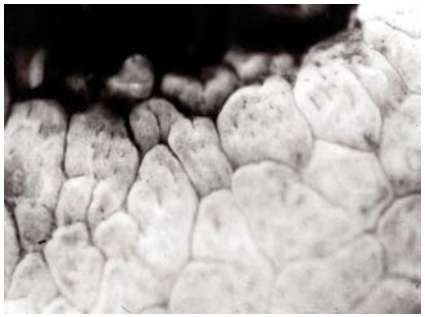


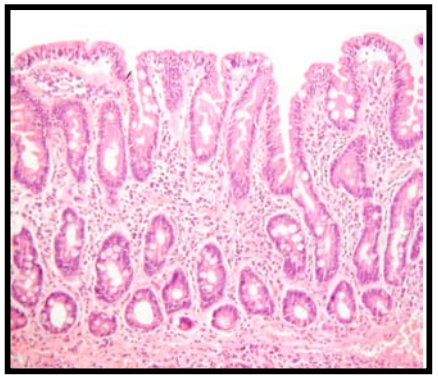


Gluten

Gluten-free diet







Treatment

- Only treatment for celiac disease is a gluten-free diet (GFD)
  - Strict, lifelong diet
  - Avoid:
    - Wheat
    - Rye
    - Barley

Dietary Adherence: A Common Problem

- Only 50% of Americans with a chronic illness adhere to their treatment regimen including:
  - diet
  - exercise
  - medication
- Dietary compliance can be the most difficult aspect of treatment

Barriers to Compliance

- Social Events – Not wanting to look/be different
- Support of Family and Friends – “Just a little bit – it won’t hurt you”
- Feelings of deprivation
- Fear generated by inaccurate information

CD patients on a GFD, no symptoms, normal serology, good compliance to the diet, but abnormal intestinal mucosa (persistent damage)

- Gray et al 2005: ~30%
- Catassi et al AJCN 2007: ~25%
- Bai et al DDW 2007: ~40%

The Future in CD is Coming

- Future potential treatments may include:
  - Development of genetically modified grains
  - Inhibitors of tissue transglutaminase
  - Cytokines and/or cytokine receptors inhibitors
  - Detoxification of immunogenic gliadin peptides via oral peptidase supplementation
  - Oral or intra-nasal celiac vaccines to induce tolerance
  - Inhibitors of the effects of zonulin on intestinal permeability

Prevention & Future Directions

Celiac Disease–Management: The Future

- Conduct a cohort study to determine the natural history of untreated celiac disease, especially “silent” celiac disease.
- Determine the response to gluten peptides in DQ2+/DQ8+ individuals without celiac disease. Determine which factors prevent disease.
- Identify which factors are involved in the induction of celiac disease in genetically susceptible individuals.
- Develop an animal model(s) of celiac disease that can be used to dissect pathogenic mechanisms.
- Determine prevalence of celiac disease in ethnic groups in the United States.
- Research prevention of celiac disease, e.g., timing of introduction of cereals in infants coupled to assessment of immune response (B-cell and T-cell) to glutens.
- Define the relationship between celiac disease and autoimmune and neuropsychiatric disorders.
- Identify non-HLA genetic modifiers that influence severity or phenotype of celiac disease.
- Develop noninvasive methodology to detect and quantify activity of celiac disease.
- Define the minimum safe exposure threshold of gluten in the diet relative to celiac disease.
- Develop alternatives to a gluten-free diet.
- Analyze the performance and cost effectiveness of serologic testing for celiac disease in the general population.
- Conduct research into screening methods for adenocarcinoma and lymphoma.
- Analyze the benefit of screening high-risk groups relevant to clinically important outcomes.
- Investigate the health-economic consequences of celiac disease.
- Identify and validate serologic assays for celiac disease diagnosis in young children.
- Investigate the quality of life of individuals with celiac disease.

***NIH Consensus Conference on Celiac Disease*, 2004.**

Research prevention of celiac disease, e.g., timing of introduction of cereals in infants

- **Although it is well established that gluten is the environmental factor needed to develop CD, the role of other dietary and environmental variables is still unclear, e.g.**
  - **Age at which gluten was first introduced**
  - **Effect of breast feeding**
  - **Amount of antigen (gluten) containing food given**
  - **Type of gluten containing food given**
  - **Role of viral infections**

HLA DQ2/DQ8 negative → STOP

At birth or at recruitment

HLA DQ2/DQ8 positive → BF or formula until 5-6 months of a
Stool collection-7d, 30d

Gluten introduction **N=515**

Not Randomized **N=63**

Group A **N=235**

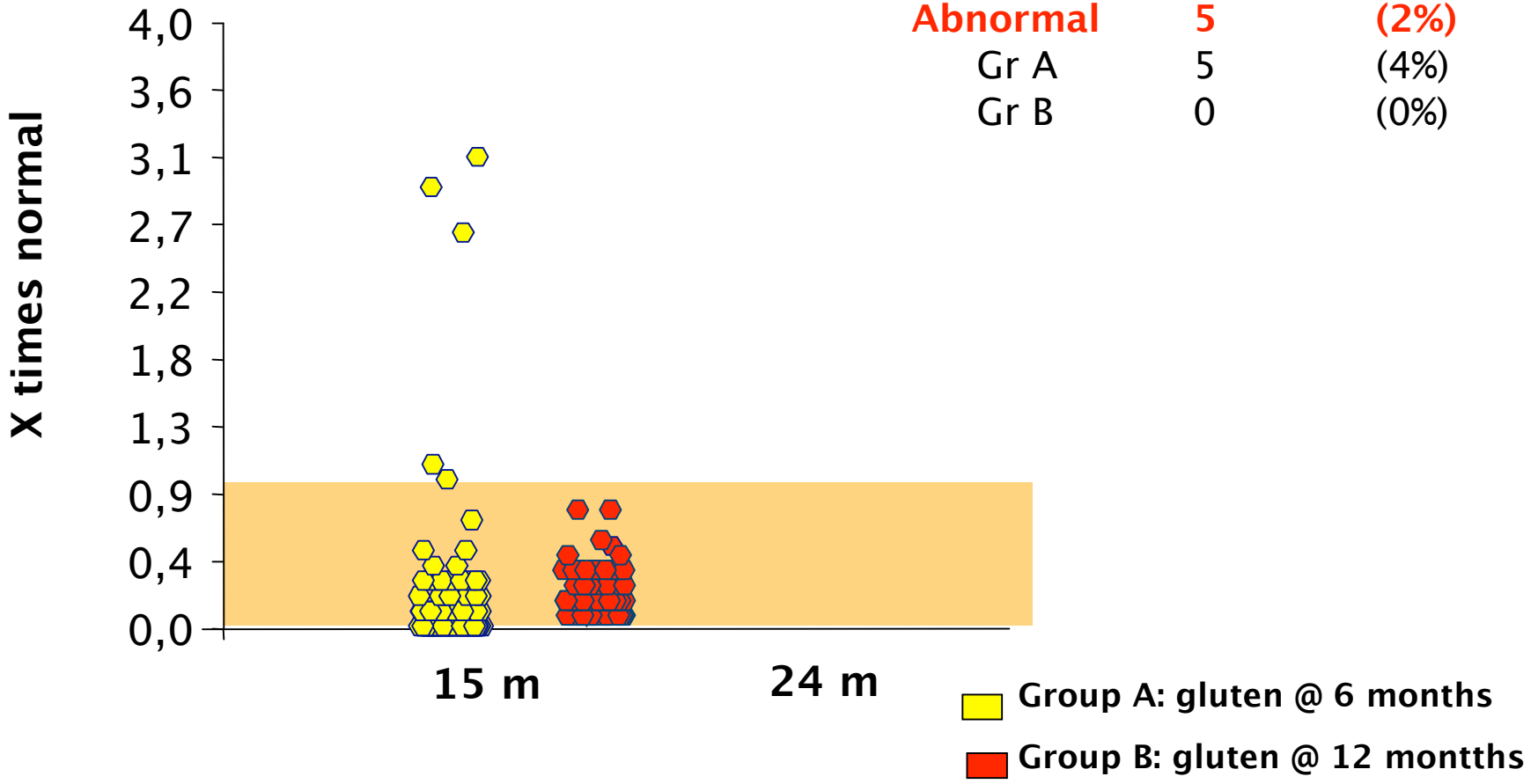
Group B **N=217**

6 months	12 months	18 months	24 months	30 months	36 months
Stool C Celiac S IPT zonulin	Stool C Celiac S IPT Zonulin Phone call	Stool C Celiac S IPT Zonulin Phone ca l	Celiac S IPT Zonulin Phone ca l	Celiac S IPT Zonulin Phone ca l	Celiac S IPT Zonulin Phone ca l

TTG-IgA 15 months (n: 210)

Normal	**205**	**(69%)**
Gr A	121	(95%)
Gr B	84	(95%)

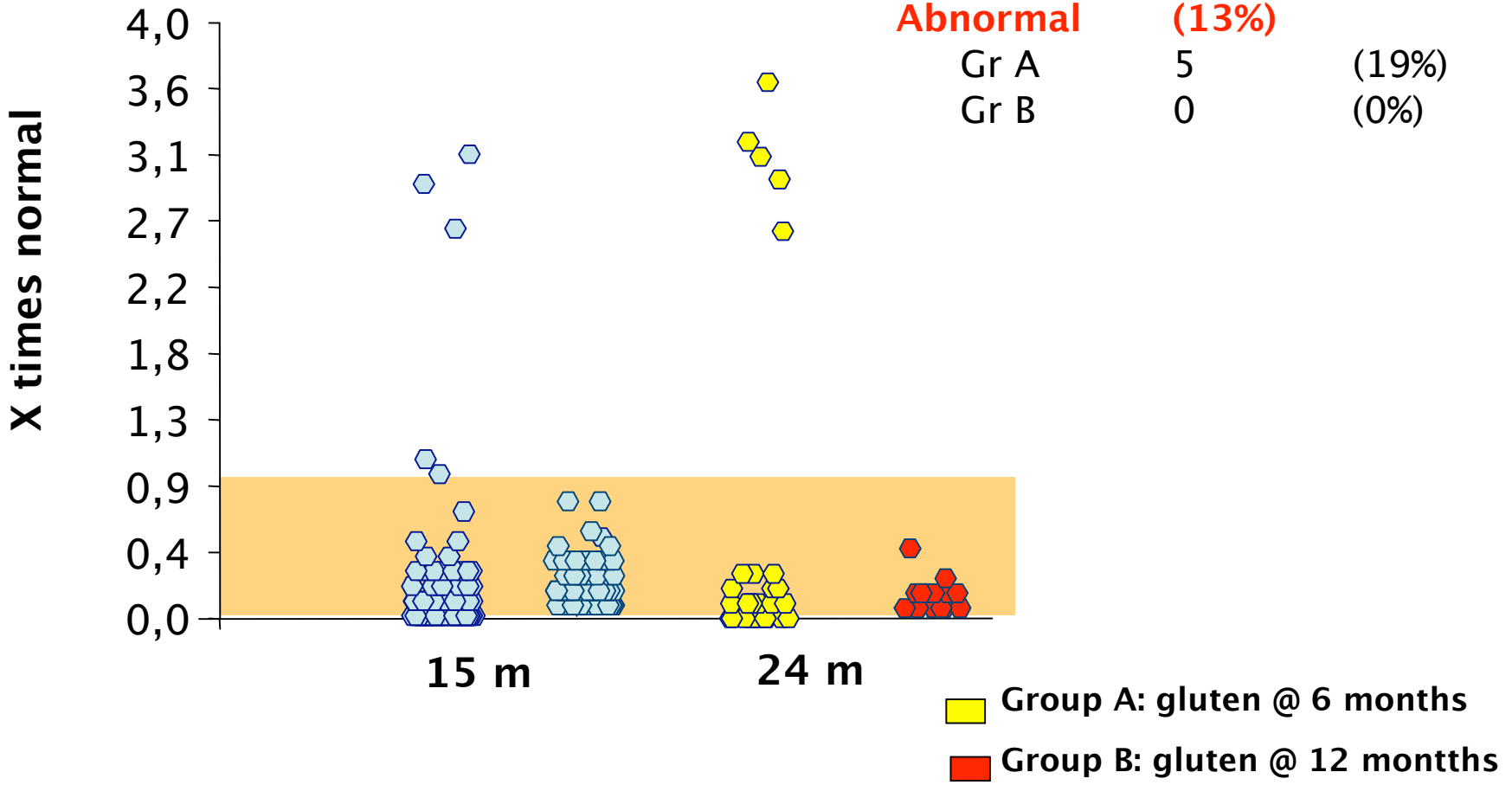
Abnormal	**5**	**(2%)**
Gr A	5	(4%)
Gr B	0	(0%)

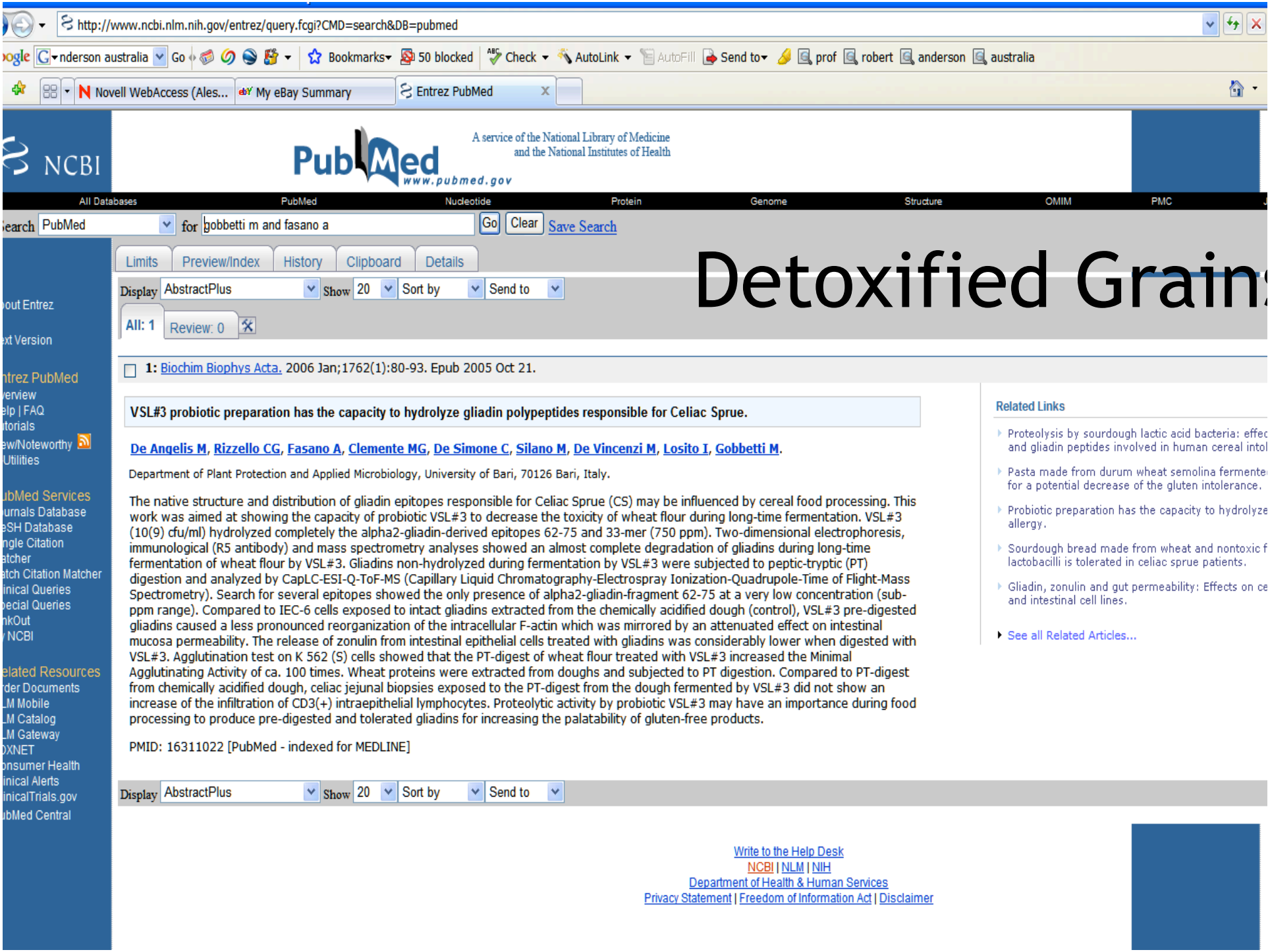


TTG-IgA 24 months (n: 45)

Normal	**40**	**(26%)**
Gr A	26	(95%)
Gr B	14	(95%)

Abnormal	**(13%)**	
Gr A	5	(19%)
Gr B	0	(0%)

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History
Clipboard
Details
Display AbstractPlus
Show 20
Sort by
Send to
All: 1
Review: 0
Detoxified Grain
1: Biochim Biophys Acta. 2006 Jan;1762(1):80-93. Epub 2005 Oct 21.
VSL#3 probiotic preparation has the capacity to hydrolyze gliadin polypeptides responsible for Celiac Sprue.
De Angelis M, Rizzello CG, Fasano A, Clemente MG, De Simone C, Silano M, De Vincenzi M, Losito I, Gobbetti M.
Department of Plant Protection and Applied Microbiology, University of Bari, 70126 Bari, Italy.
The native structure and distribution of gliadin epitopes responsible for Celiac Sprue (CS) may be influenced by cereal food processing. This work was aimed at showing the capacity of probiotic VSL#3 to decrease the toxicity of wheat flour during long-time fermentation. VSL#3 (10(9) cfu/ml) hydrolyzed completely the alpha2-gliadin-derived epitopes 62-75 and 33-mer (750 ppm). Two-dimensional electrophoresis, immunological (R5 antibody) and mass spectrometry analyses showed an almost complete degradation of gliadins during long-time fermentation of wheat flour by VSL#3. Gliadins non-hydrolyzed during fermentation by VSL#3 were subjected to peptic-tryptic (PT) digestion and analyzed by CapLC-ESI-Q-ToF-MS (Capillary Liquid Chromatography-Electrospray Ionization-Quadrupole-Time of Flight-Mass Spectrometry). Search for several epitopes showed the only presence of alpha2-gliadin-fragment 62-75 at a very low concentration (sub-ppm range). Compared to IEC-6 cells exposed to intact gliadins extracted from the chemically acidified dough (control), VSL#3 pre-digested gliadins caused a less pronounced reorganization of the intracellular F-actin which was mirrored by an attenuated effect on intestinal mucosa permeability. The release of zonulin from intestinal epithelial cells treated with gliadins was considerably lower when digested with VSL#3. Agglutination test on K 562 (S) cells showed that the PT-digest of wheat flour treated with VSL#3 increased the Minimal Agglutinating Activity of ca. 100 times. Wheat proteins were extracted from doughs and subjected to PT digestion. Compared to PT-digest from chemically acidified dough, celiac jejunal biopsies exposed to the PT-digest from the dough fermented by VSL#3 did not show an increase of the infiltration of CD3(+) intraepithelial lymphocytes. Proteolytic activity by probiotic VSL#3 may have an importance during food processing to produce pre-digested and tolerated gliadins for increasing the palatability of gluten-free products.
PMID: 16311022 [PubMed - indexed for MEDLINE]
Related Links
Proteolysis by sourdough lactic acid bacteria: effec and gliadin peptides involved in human cereal intol
Pasta made from durum wheat semolina fermente for a potential decrease of the gluten intolerance.
Probiotic preparation has the capacity to hydrolyze allergy.
Sourdough bread made from wheat and nontoxic f lactobacilli is tolerated in celiac sprue patients.
Gliadin, zonulin and gut permeability: Effects on ce and intestinal cell lines.
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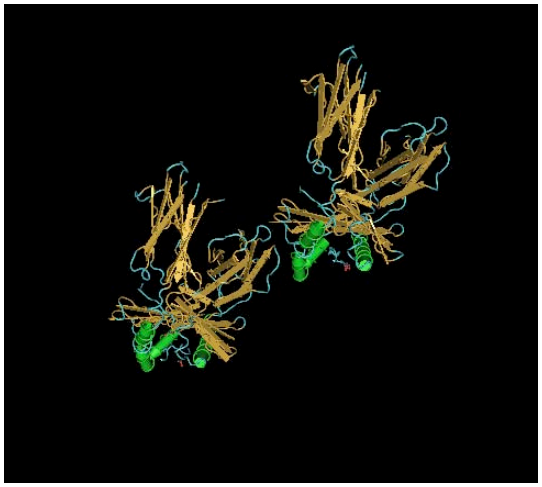
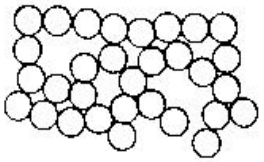
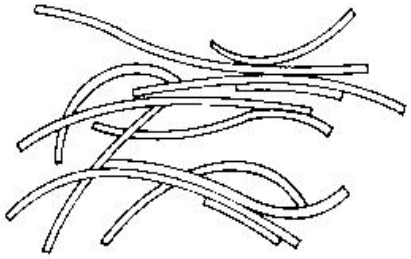
What is so Special About Gluten?

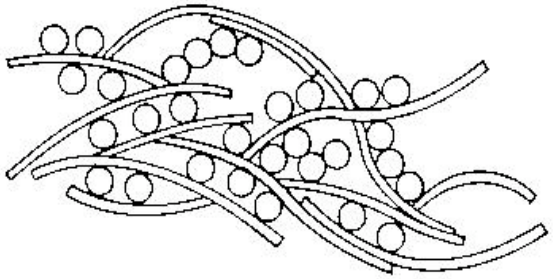




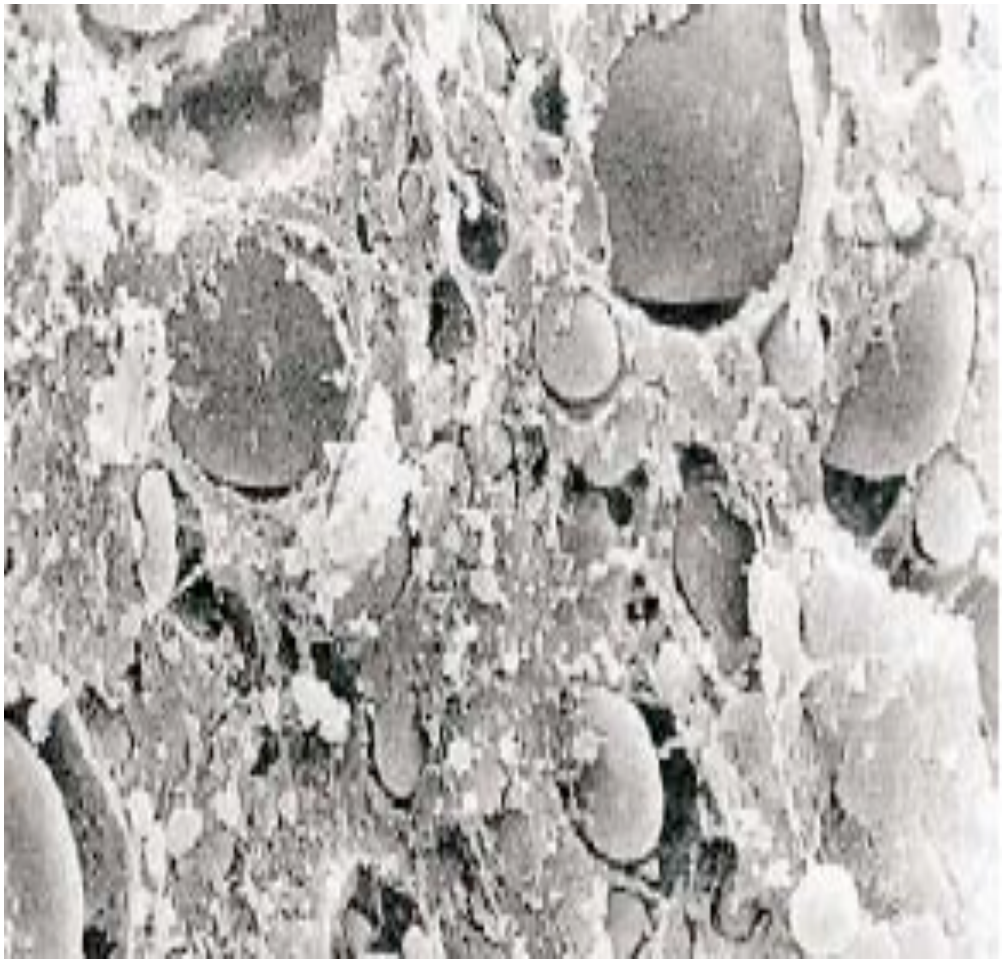
Gliadin



Glutenin



Gluten (gliadin+glutenin)



Vaccine

1: Gut. 2006 Apr;55(4):485-91. Epub 2005 Nov 18.

Antagonists and non-toxic variants of the dominant wheat gliadin T cell epitope in coeliac disease.

Anderson RP, van Heel DA, Tye-Din JA, Jewell DP, Hill AV.

Autoimmunity and Transplantation Division, Walter and Eliza Hall Institute, Department of Gastroenterology, The Royal Melbourne Hospital, Parkville, Victoria, Australia. banderson@wehi.edu.au

BACKGROUND: Coeliac disease (CD) is due to an inappropriate T cell mediated response to specific gluten peptides. Measured by interferon gamma (IFN-gamma) ELISPOT, about half of the gliadin specific T cells induced with in vivo wheat gluten exposure in HLA-DQ2+ CD are specific for an alpha/beta-gliadin peptide (p57-73 QE65; QLQPFPQPELPYPQPQS) that includes two overlapping T cell epitopes (PFPQPELPY and PQPELPYPQ). AIM: To define minimally substituted variants of p57-73 QE65 universally devoid of IFN-gamma stimulatory capacity but capable of antagonising IFN-gamma secretion from polyclonal T cells specific for p57-73 QE65. METHODS: Peripheral blood mononuclear cells collected from 75 HLA-DQ2+ CD patients after in vivo gluten challenge were used in overnight ELISPOT assays to screen 218 single or double substituted variants of p57-73 QE65 for cytokine stimulatory and antagonist activity. RESULTS: The region p60-71 (PFPQPELPYPQP) and especially p64-67 (PELP) was sensitive to substitution. Twelve substitutions in p64-67 stimulated no IFN-gamma ELISPOT response. Among 131 partial agonists identified, 45 produced statistically significant inhibition of IFN-gamma ELISPOT responses when cocultured in fivefold excess with p57-73 QE65 (n = 10). Four substituted variants of p57-73 QE65 were inactive by IFN-gamma ELISPOT but consistently antagonised IFN-gamma ELISPOT responses to p57-73 QE65, and also retained interleukin 10 stimulatory capacity similar to p57-73 QE65. CONCLUSIONS: Altered peptide ligands of p57-73 QE65, identified using polyclonal T cells from multiple HLA-DQ2+ CD donors, have properties in vitro that suggest that a single substitution to certain alpha/beta-gliadins could abolish their capacity to stimulate IFN-gamma from CD4 T cells and also have anti-inflammatory or protective effects in HLA-DQ2+ CD.

PMID: 16299041 [PubMed - indexed for MEDLINE]

Related Links
T cells in peripheral blood after gluten c
In vivo antigen challenge in celiac disea as the dominant A-gliadin T-cell epitope
IgA antibodies of coeliac disease patien
Investigation of the putative immunodo
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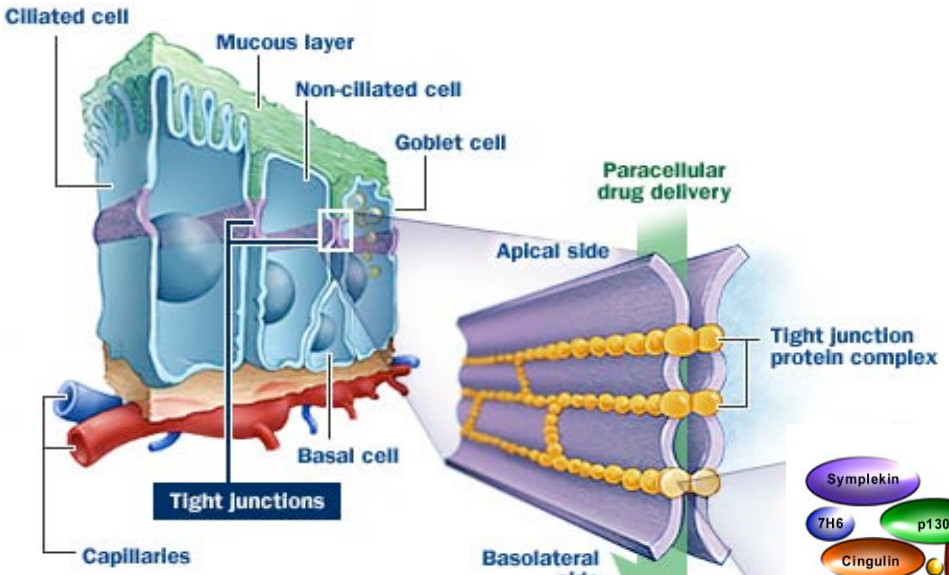
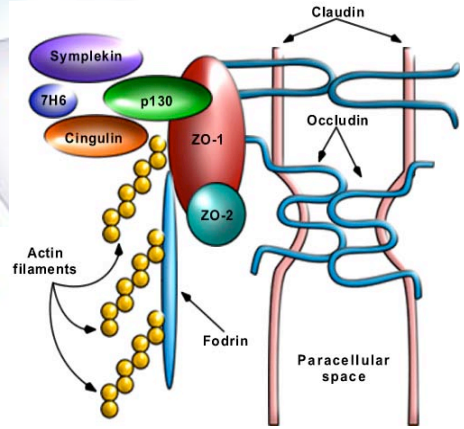
The Anti-Zonulin Pill: Facts and Fantasies

The Paracellular Pathway





Journal of Cell Science 113, 4435-4440 (2000)
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JCS1508

Human zonulin, a potential modulator of intestinal tight junctions

Wenle Wang[1], Sergio Uzzau[1], Simeon E. Goldblum[2] and Alessio Fasano[1,3,*]

[1]Division of Pediatric Gastroenterology and Nutrition and Gastrointestinal Pathophysiology Section, Center for Vaccine Development, [2]Division of Infectious Diseases, Department of Veterans Affairs Medical Center and [3]Department of Physiology, University of Maryland, School of Medicine, Baltimore, Maryland 21201, USA

*Author for correspondence at address 1 (e-mail: afasano@umaryland.edu)

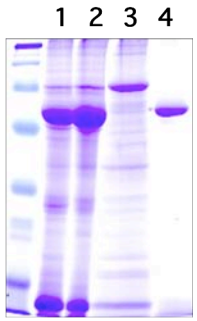
PURIFICATION PROTOCOL FROM HUMAN INTESTINE

1: Tissue lysate

2: Sephacryl- S300

3: Q - sepharose

4: Immuoaffinity



Coomassie

Western blot

…Tight junctions are a 'dark horse' implicated in a host of disease states, ranging from acute injury to chronic inflammation and autoimmune diseases

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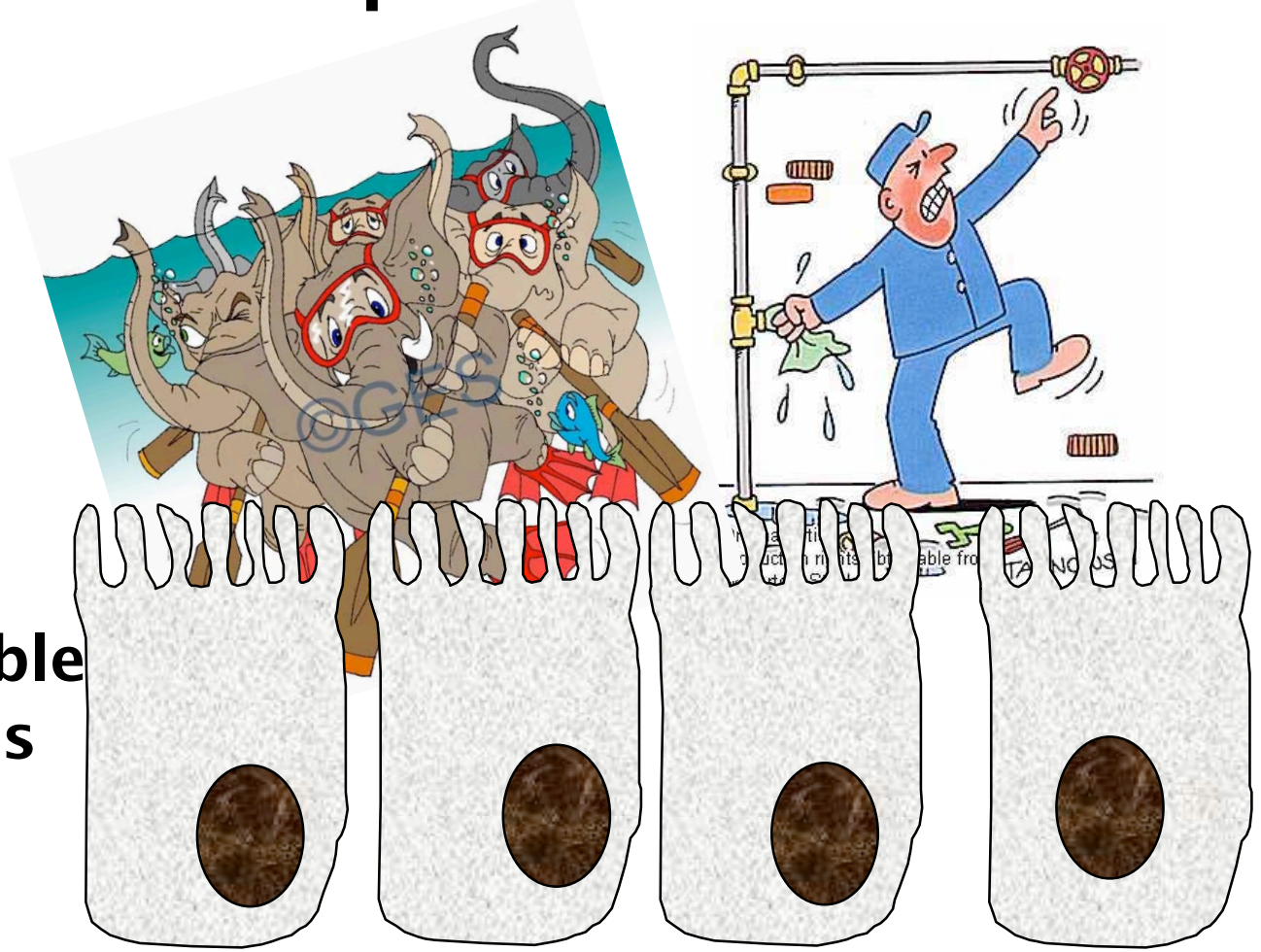
Absorption of gluten peptides: Mission Impossible

Environment



Barrier impermeable to macromolecules

Gene load

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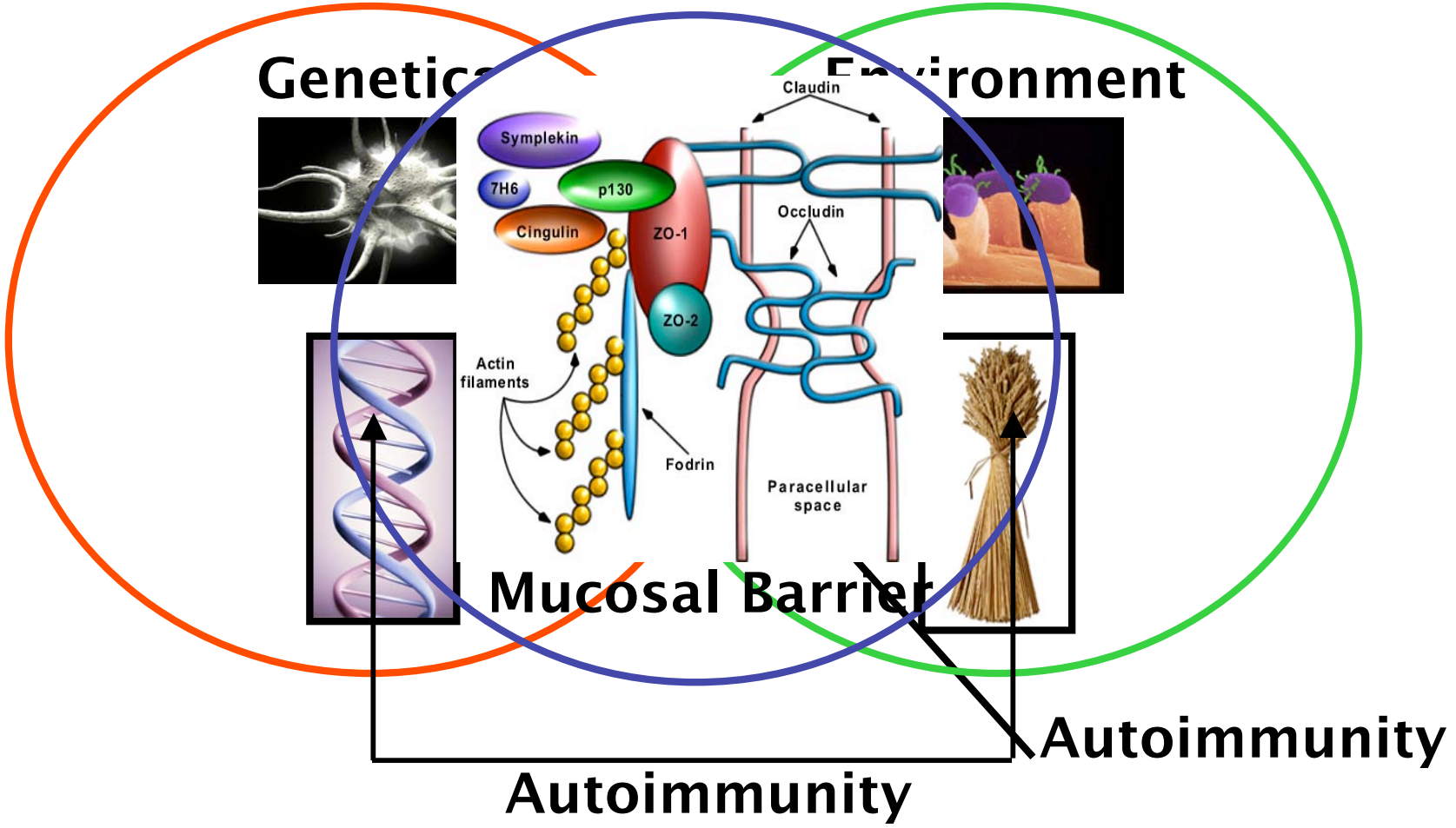
Novel Paradigm for Autoimmunity

Autoimmune diseases involve a miscommunication between innate and adaptive imm



- **A third key element necessary to develop autoimmunity is the loss of the mucosal barrier function, so allowing the interplay between genes and environment.**

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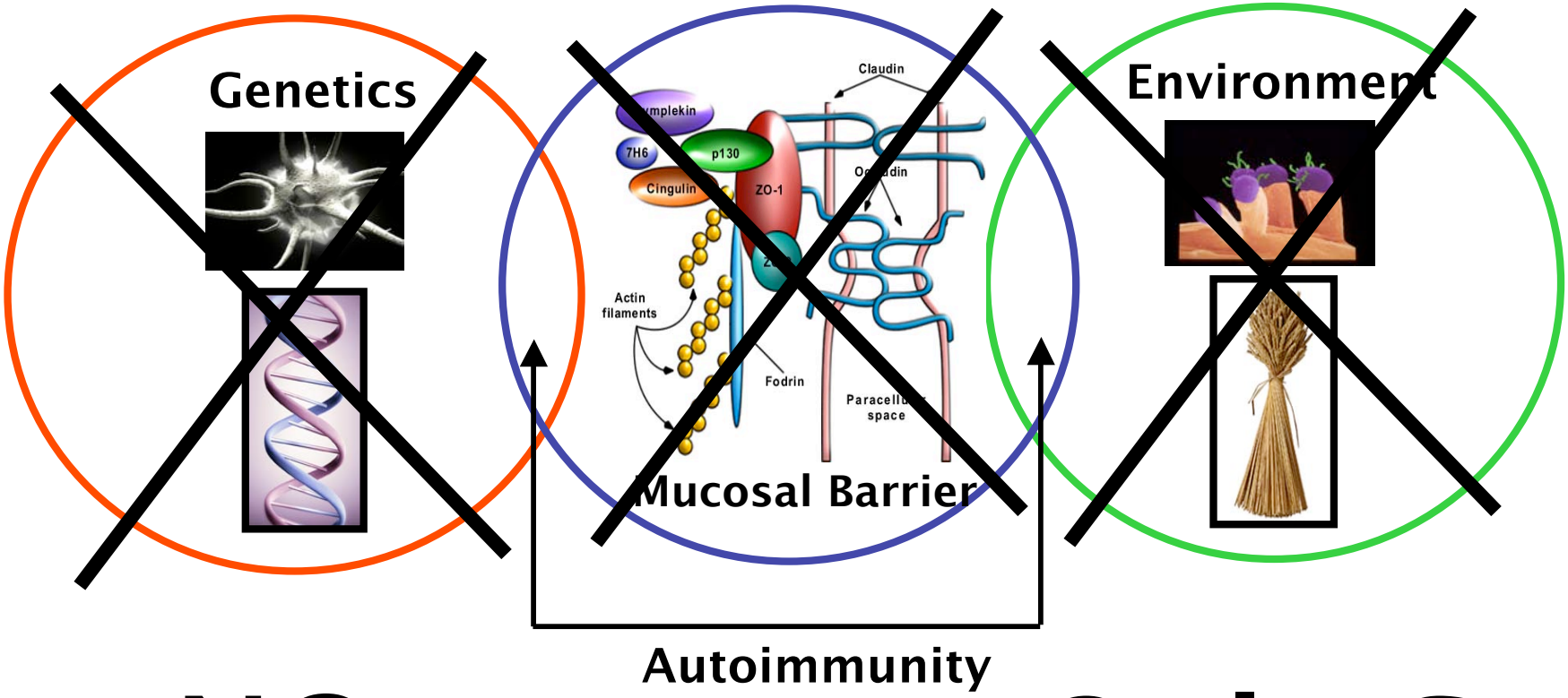
Fasano A. Shea-Donoue T. Nat Clin Pract Gastroenterol Hepatol. 2005;2:416

Prove of Concept on Alternative Treatments of Autoimmune Diseases



NO **?** **Only CD**

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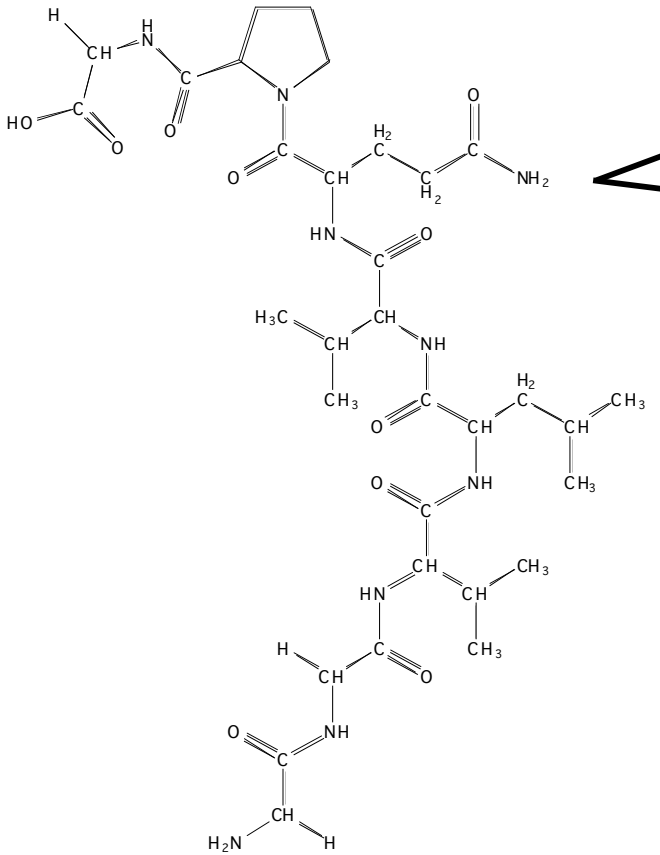
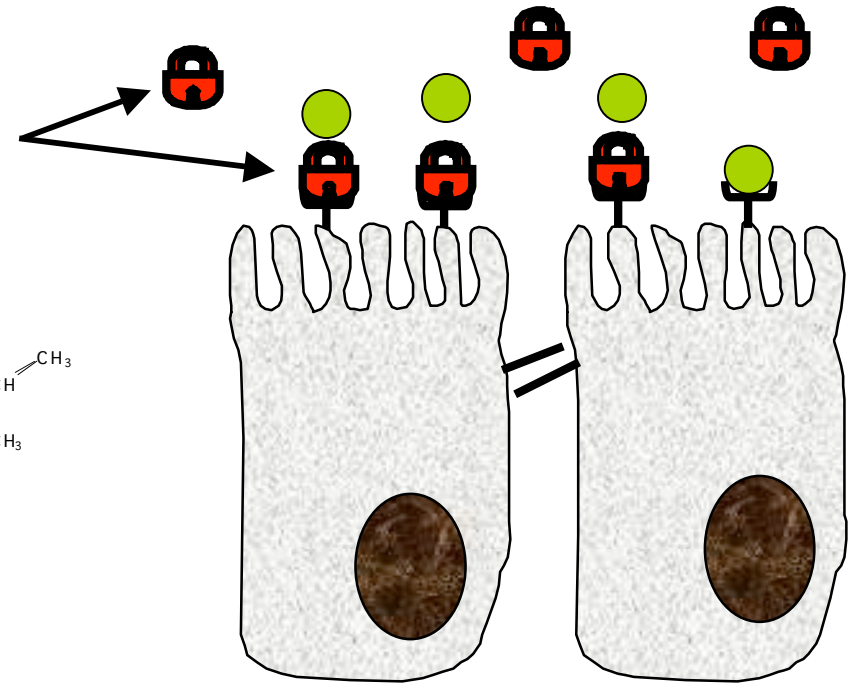
AT-1001, the Zonulin Inhibitor



$C_{32}H_{55}N_9O_{10}$
Exact Mass: 725.41
Mol. Wt.: 725.83
m/e: 725.41 (100.0%), 726.41 (35.6%), 727.41 (9.2%), 726.40 (3.3%)
C, 52.95; H, 7.64; N, 17.37; O, 22.04



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Di Pierro et al, J Biol Chem 2001;276:19160

Drug Development Pipeline

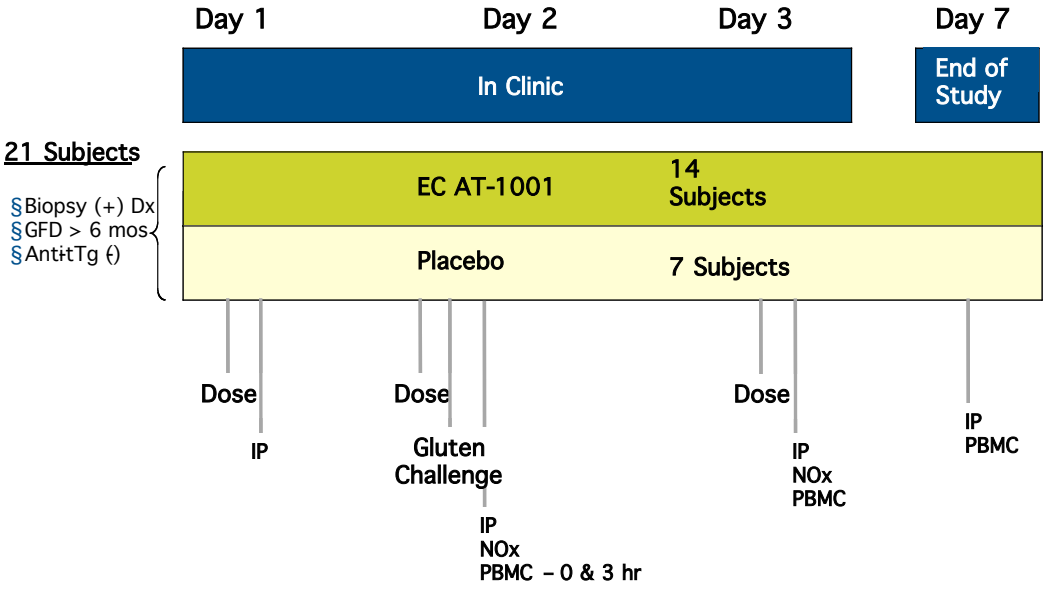
Steps	Nr Products
v Potential drugs discovered and tested in the lab	1000
v Experiments on animals to verify safety	600
v IND application to the FDA for human trials	300
v Clinical trials to verify safety and efficacy	200
v Fase 1	100
v Fase 2	50
v Fase 3	20
v Application to the FDA for approval for clinical use	2-3

- Timeline: 15-20 years
- Costs: $ 800M - 1B

Human Studies

Phase Ib, celiac disease

A



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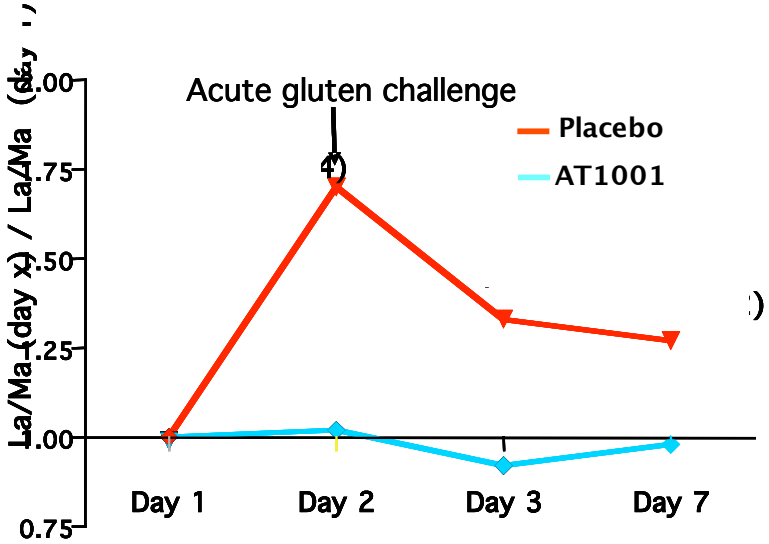

C

Gastrointestinal Disorders	Subject Count (%) By Treatment		P-Value
	Placebo (N=7)	AT-1001 (N=14)	(Fisher's exact test)
Total	7 (100%)	6 (43%)	0.018
Abdominal Discomfort	2 (29%)	0 (0%)	0.10
Constipation	1 (14%)	0 (0%)	0.33
Diarrhea	**5 (71%)**	**2 (14%)**	**0.017**
Flatulence	2 (29%)	2 (14%)	0.57
Vomiting	1 (14%)	3 (21%)	1.0

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Paterson et al. in press

AT-1001 Clinical Trials Summary

- Phase I, Single Dose Safety Study (CLIN1001-001a)
  - 24 Healthy Volunteers
  - Completed, October 2005

- Phase Ib, POC, Single-Dose, Proof of Concept (CLIN1001-002)
  - 21 celiac disease subjects
  - Completed, March 2006
  - Double blind, placebo controlled
  - 3 days dosing, single gluten challenge day 2
  - Achieved clinical proof of concept

- Phase I, Multi-Dose Safety Study (CLIN1001-003)
  - 24 Healthy Volunteers
  - Completed, April 2006

- Phase II, Multi-Dose Proof of Concept (CLIN1001-004)
  - 86 celiac disease subjects, enrollment completed 13th February 2007, unblinded May 15th
  - Double blind, placebo controlled
  - Dose ranging, 7 arms, 2 weeks dosing

- Phase IIb Multi-Dose Proof of Efficacy (CLIN1001-006)
  - 180 celiac disease subjects to be enrolled, 145 already enrolled
  - Projected date of completion: October 2008

The "anti-zonulin pill": The Roadmap from DISCOVERY/DEVELOPMENT to PRODUCTION/DEVELOPMENT

Start

Initial Discussion FDA (2005) 3 months

Preclinical Studies ADME, Tox, Biology 12-24 months

File Celiac IND, request ast track 6 month s

Single Dose Toxicity & PK, SDSS 6 months

↓ Intestinal Permeab?

No

Yes

Reformulate

File results 6 months

4 weeks Multiple Doses Tox Doses 12 months

Completed May 2007

Phase II 2 months. Doses range 12 months

October 2008

End Phase II Meeting; confirm Fast track

Pivotal #1 Celiac 24 months

Pivotal #2 Celiac 24 months

Celiac Disease NDA 7 years total

To learn more:
www.albatherapeutics.com

Treatments Alternative to a GFD:

Predicted Timeline