



Celiac Disease: Immunology 101 and the Drug Development Process



with

Ken Kilgore MS, PhD and Francisco Leon MD, PhD of Janssen Pharmaceuticals

June 11, 2013



Important Reminders!

① Will this information be available at a later date?

- Yes, always!
- **Webinar recording will be posted along with the webinar slides within 72 hours after the live webinar ends.** Download recorded webinars and slides at the Archived Webinars page: CeliacCentral.org/webinars/archive/

② Are continuing education credits available?

- Yes!
- NFCA will provide a certificate as proof of participation for each webinar. **Attendees must complete the follow-up survey in order to access this certificate. Program participants will receive a link to complete the follow-up survey on Friday, June 14th through an email from NFCA.**
- **To ensure that you receive this email, make sure that NFCA (National_Foundation_for_Celiac_A@gmail.vresp.com) is on your allowed senders list.** If you have unsubscribed from any NFCA emails, please register for the webinar with a new email address. Make sure your email address is spelled correctly when registering, as we will use this for our follow-up communications.
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- Each participant must register for and log in to the webinar in order to receive credit. **In the case of group viewing, only the registered and logged in participant will receive credit for the webinar.**





More News

- New NFCA contact info: webinars@celiaccentral.org
- Interview with Joseph Murray, MD on the current landscape of non-dietary treatments for celiac disease
- New section on website: “Drug Development and Clinical Trials”





Watch & Win!

- Five winners will receive prize pack from NFCA:
 - NFCA t-shirt
 - NFCA lunch tote
 - NFCA plastic water bottle





Welcome!

Ken Kilgore, MS, PhD



- Leads ImmunoPharmacology Group in Immunology Therapeutic Area at Janssen Pharmaceuticals of Johnson & Johnson
- Joint faculty appointment in Pharmacology and Cardiovascular Surgery Departments, University of Michigan
- Formerly with Pfizer and GlaxoSmithKline
- Author of more than 60 scientific publications and numerous book chapters
- Executive of NFCA Scientific/Medical Advisory Council





Welcome!

Francisco Leon, MD, PhD



- Vice President of Immunology Translational Medicine at Janssen Pharmaceuticals of Johnson & Johnson
- Clinical immunologist trained in Spain and at the National Institutes of Health (NIH)
- Areas of focus:
 - Basic research: Mucosal immunology and celiac disease
 - Biotech and pharmaceutical: Spans most areas of early development in immunology
- Formerly with Bristol-Myers Squibb and MedImmune
- Former Chief Medical Officer of Alba Therapeutics



On Today's Plate

- ① Explain the immunological process of celiac disease
- ② Identify reasons why a non-dietary pharmaceutical therapy is needed for celiac disease
- ③ Describe the stages of the FDA's drug development and approval process
- ④ Discuss the role patients play in clinical trials





Celiac Disease Primer



- Chronic inflammatory disease
- Response initiated by dietary gluten
- Primarily impacts small intestine
- Leads to bowel structural damage
- Associated with multiple conditions

<http://ibstreatmentcenter.com/2011/02/ceciac-disease-q-from-sun.html>

Two Arms: Innate vs. Adaptive Immunity

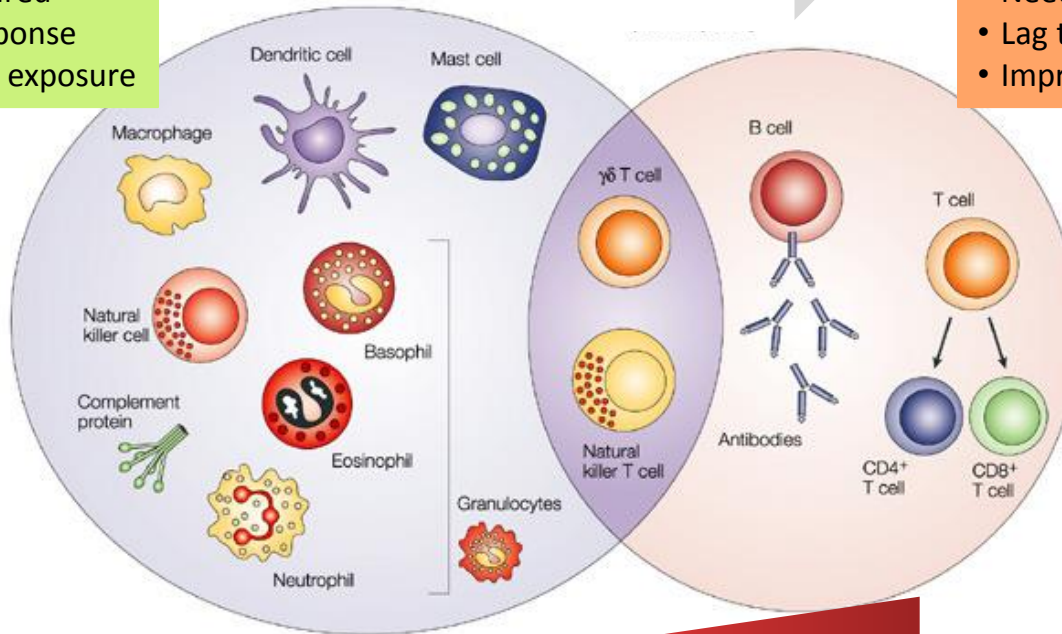
Innate:

- General Protection
- Early phase (rapid response)
- Prior exposure not required
- Immediate maximal response
- Not altered by repeated exposure

Hours

Days

Time Post-Infection

Adaptive:

- Specific for a pathogen
- Late phase
- Need prior exposure
- Lag time
- Improves with each exposure

Modified from:

http://www.nature.com/nrc/journal/v4/n1/fig_tab/nrc1252_F1.html

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Role in Celiac Disease

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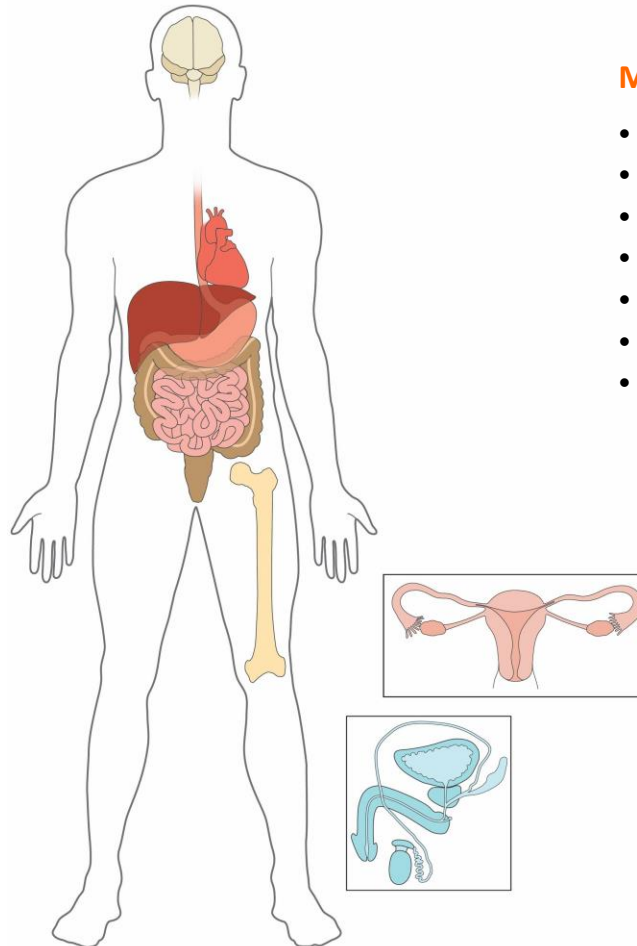
An immune disease, by its very nature...

Central Nervous System:

- Ataxia, seizures
- Developmental delays
- Depression
- “Brain fog”

Cardiovascular System:

- Cardiomyopathy



Muscular, Skeletal and Dental Systems:

- Osteopenia and osteoporosis
- Osteomalacia and rickets
- Arthritis
- Short status
- Hypotonia
- Muscle cramps and wasting
- Dental enamel defects

Reproductive System:

- Infertility
- Miscarriage
- Delayed puberty



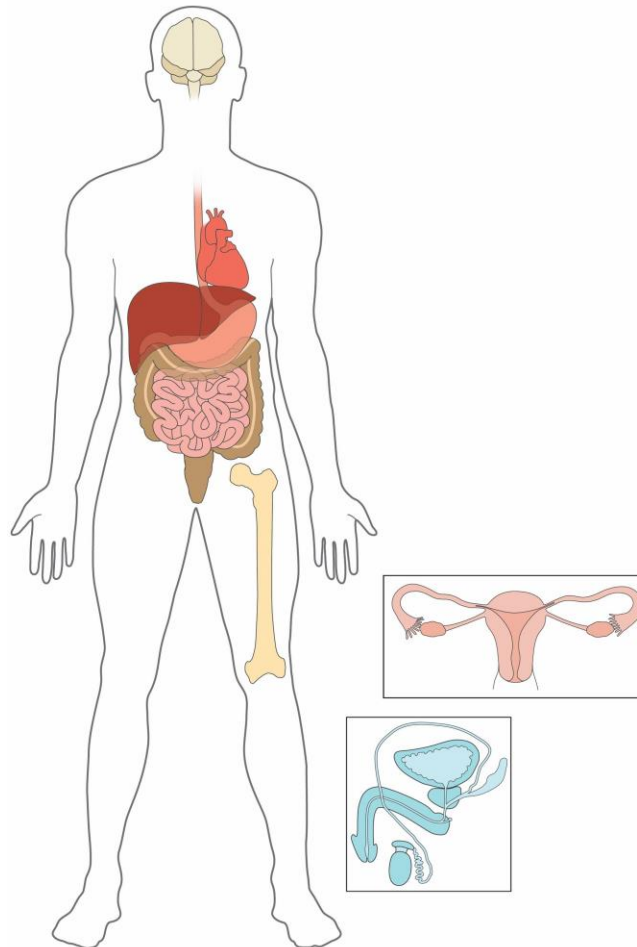
An immune disease, by its very nature...

General:

- Anemia
- Fatigue
- Irritability
- Failure to thrive

Skin and Mucosal Systems:

- Dermatitis herpetiformis
- Aphthous stomatitis
- Alopecia



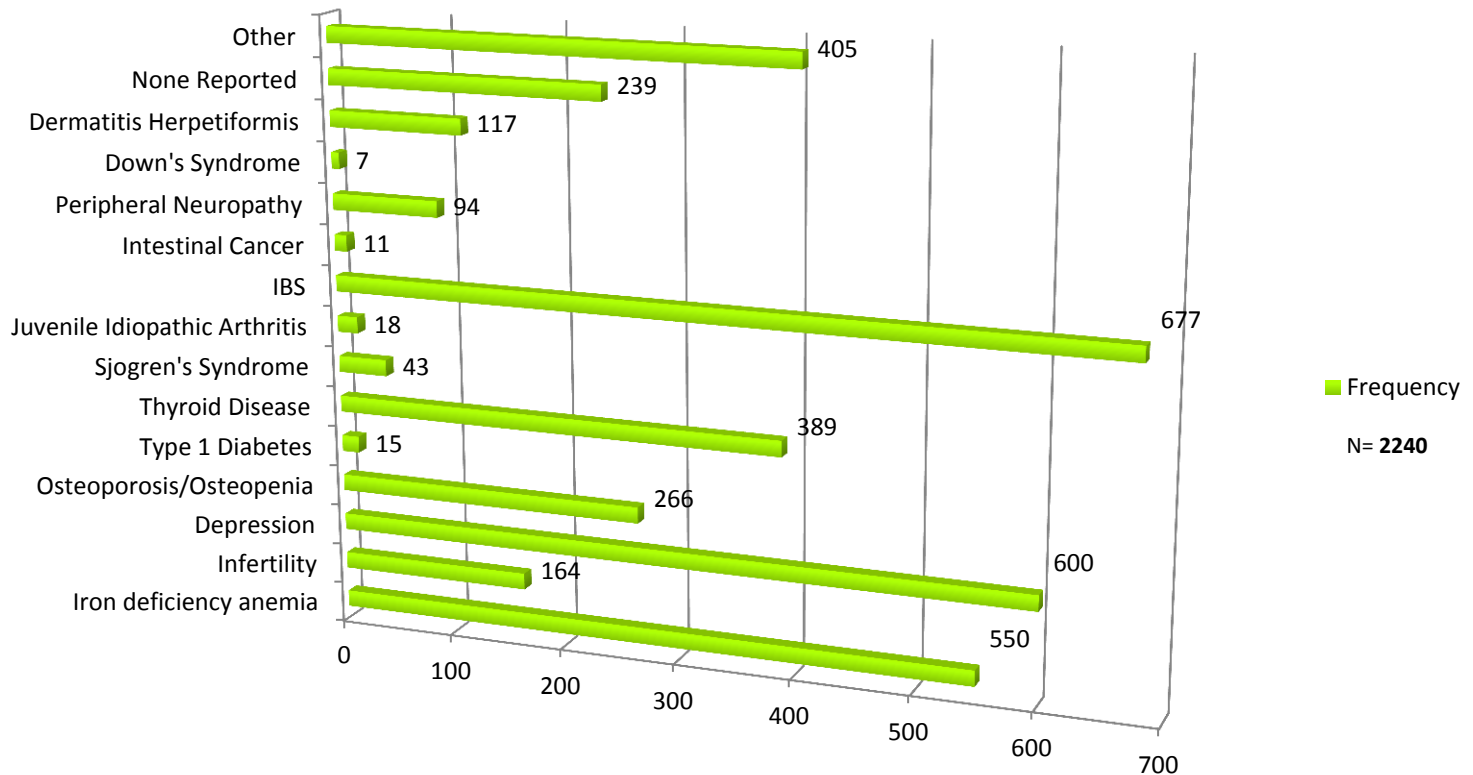
GI System:

- Diarrhea
- Constipation
- Vomiting
- Malnutrition
- Weight loss or weight gain
- Abdominal pain and distention
- Malignancies
- Hepatitis cholangitis



What do these people experience?

Have you been diagnosed with any of the following conditions?



NFCA Celiac Disease Symptoms Checklist, March 2009 – May 2011





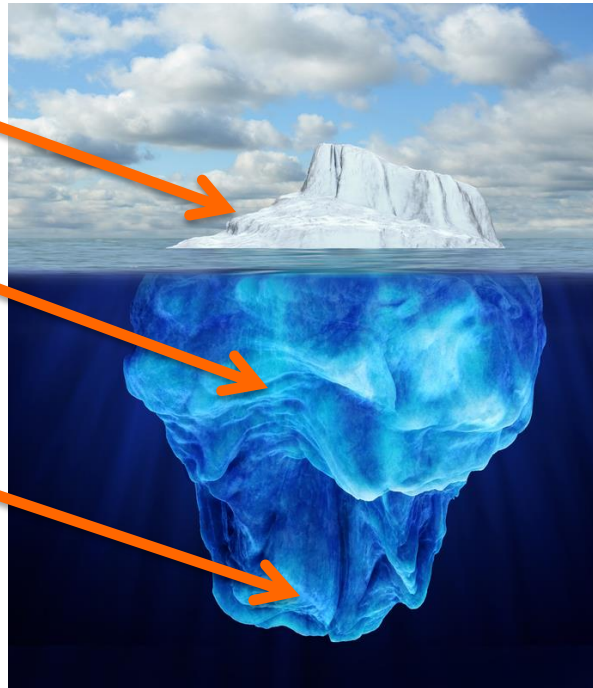
Diagnosed Celiac Disease Represents the Tip of the Iceberg

“Celiac Iceberg”

Symptomatic
Celiac Disease

Asymptomatic and Subclinical
Celiac Disease

Potential Celiac Disease



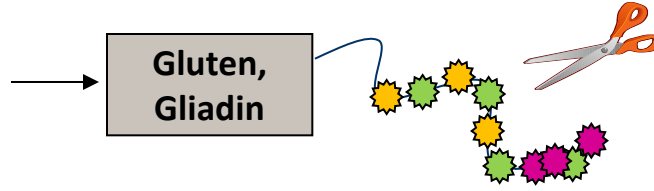
Questions and Challenges:

- Likely a much larger number of people with *asymptomatic* and/or *subclinical* celiac disease
- What is the degree of intestinal damage?
- What about “hidden” nutritional deficiencies (i.e. iron deficiency anemia)?
- Do some have potential celiac disease?



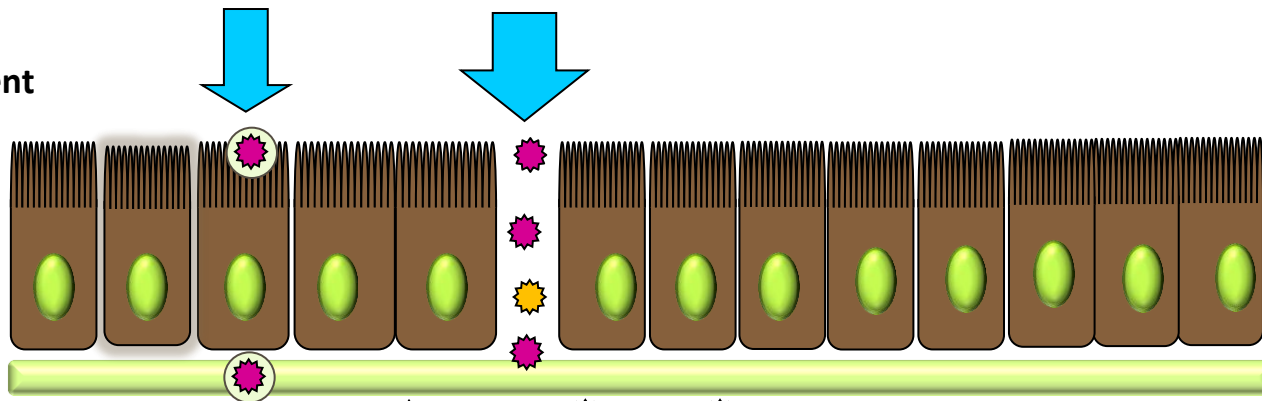
Celiac Disease Pathogenesis (1)

Wheat



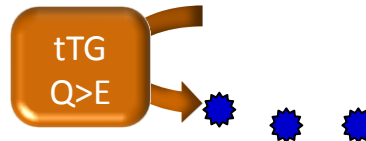
Incomplete digestion in the gut

Gut content



Gut wall

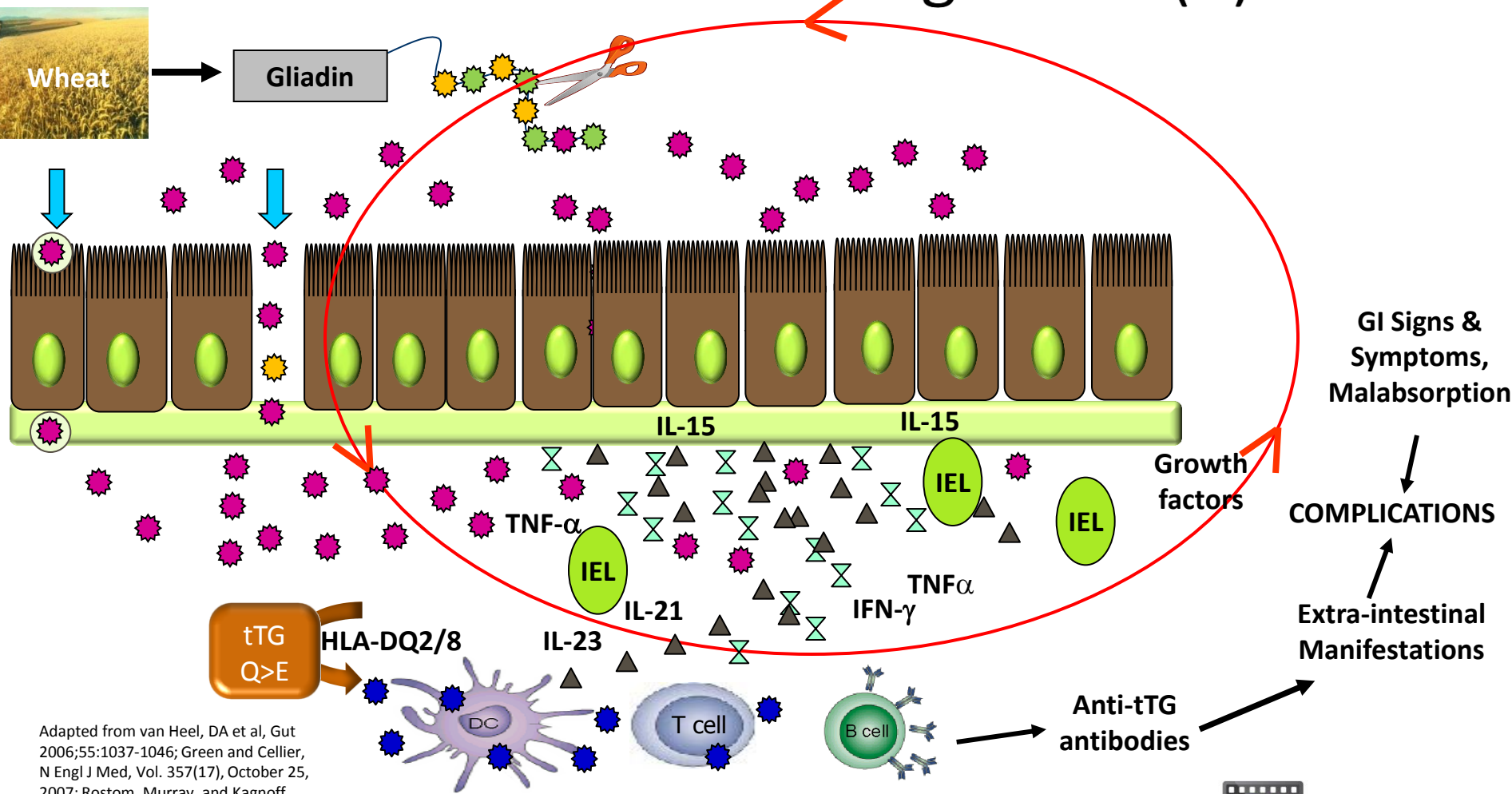
Tissue-transglutaminase (tTG) enzyme



Adapted from van Heel, DA et al, Gut 2006;55:1037-1046; Green and Cellier, N Engl J Med, Vol, 357;17 October 25, 2007

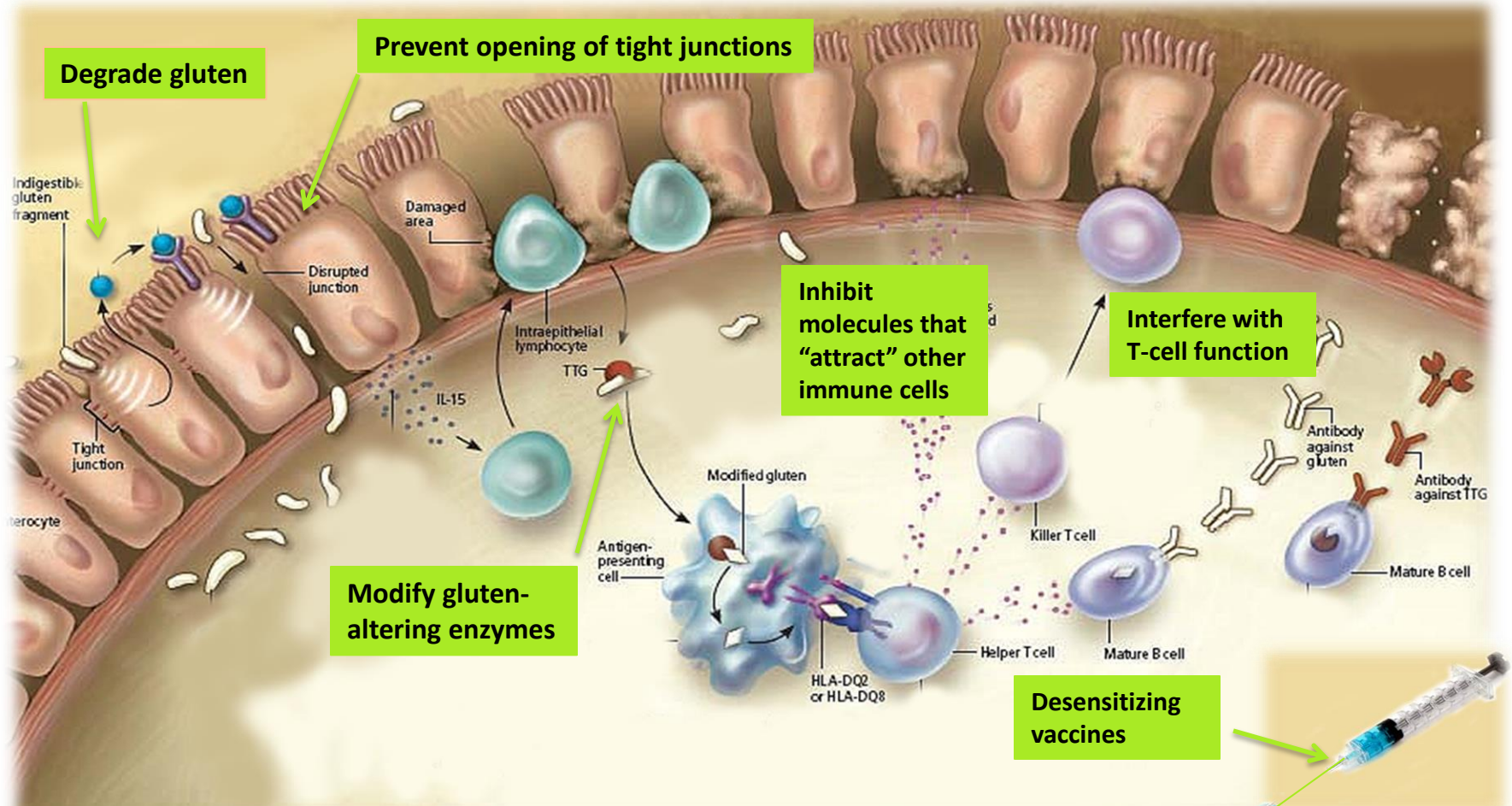


Celiac Disease Pathogenesis (2)



Adapted from van Heel, DA et al, Gut 2006;55:1037-1046; Green and Cellier, N Engl J Med, Vol. 357(17), October 25, 2007; Rostom, Murray, and Kagnoff, Gastroenterology, Vol.131, 2001

Potential Ways to Treat Celiac Disease



Modified from: Fasano, A. Scientific American; v:301; 54-61; 2009.

http://www.nature.com/scientificamerican/journal/v301/n2/box/scientificamerican0809-54_BX3.html

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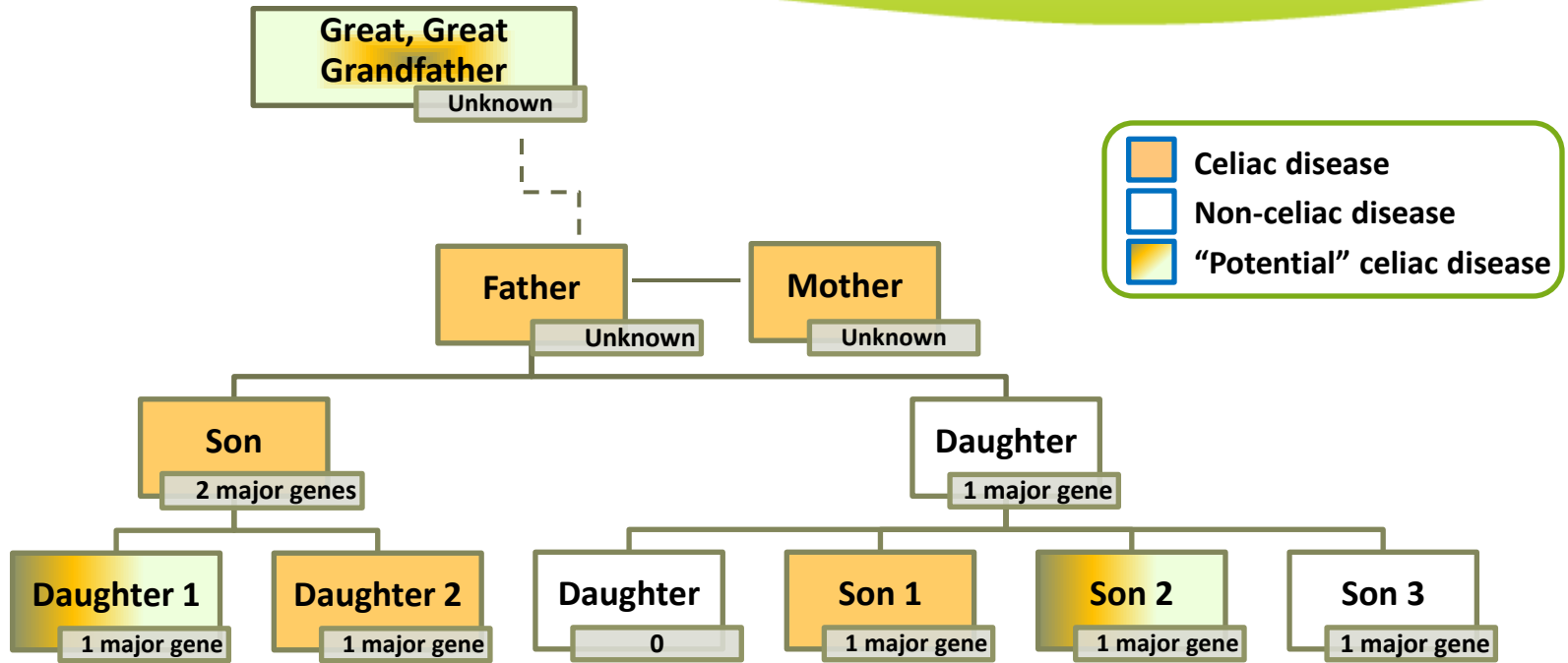
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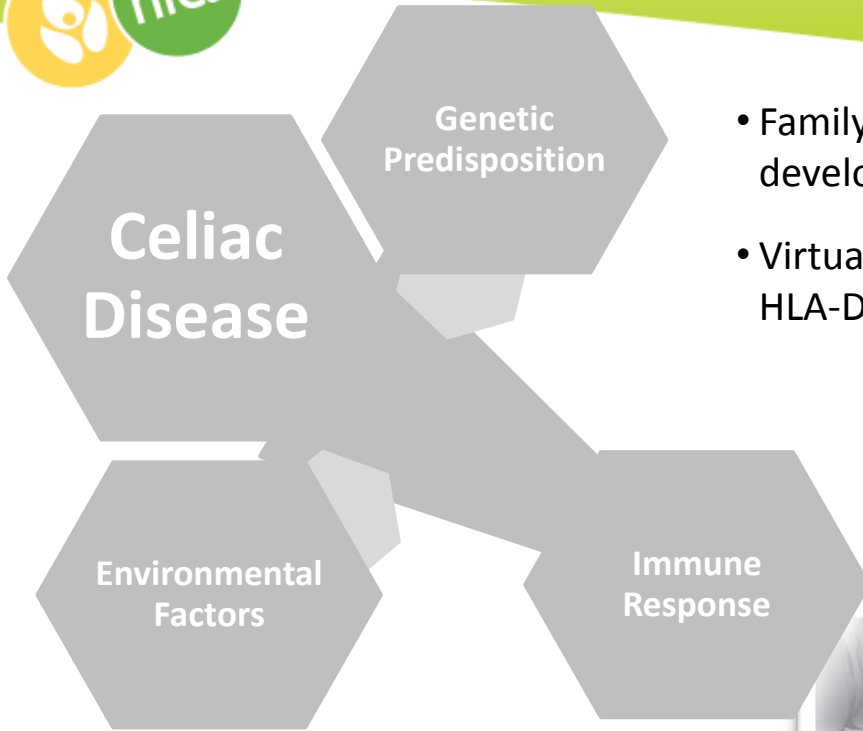
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Celiac Disease: It's All in the Family

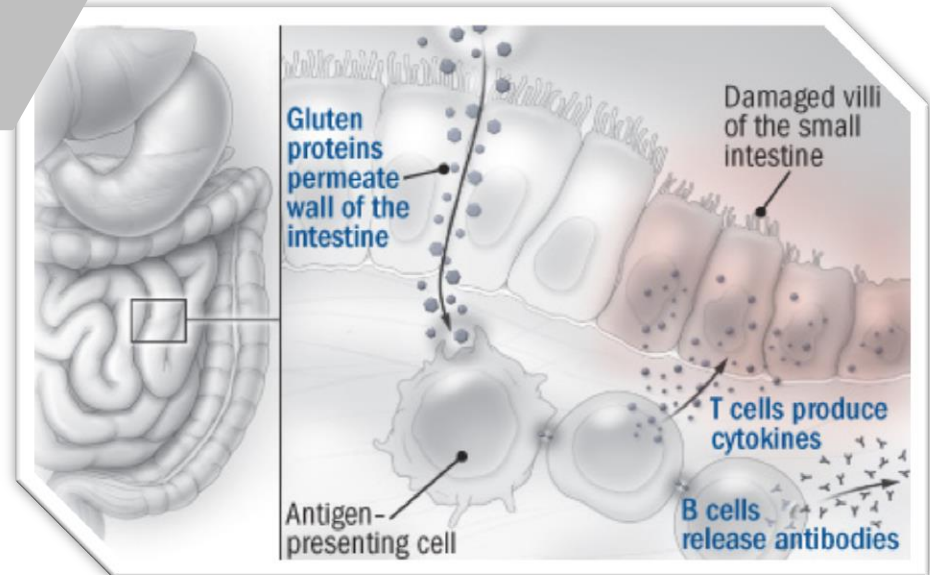




- Family members of celiac patients are at higher risk of developing celiac disease
- Virtually all individuals with celiac disease have HLA-DQ2 or HLA-DQ8

• Exposure to cereal grain proteins:

- Wheat
 - Barley
 - Rye
- } Gluten





Why is a pharmaceutical therapy needed for celiac disease?

- Challenges with the gluten-free diet:
 - Adherence
 - Burden of treatment
 - Ease and convenience
 - Cost
 - Risk of cross-contamination/cross-contact
 - Lack of food labeling
 - Food-stuff testing
- Ongoing symptoms despite diet adherence
- Lack of consistent mucosal healing (morbidity and mortality)

Non-dietary therapeutic clinical trials in coeliac disease, Laura Crespo Pérez, Gemma Castillejo de Villasante, Ana Cano Ruiz, Francisco León, *European Journal of Internal Medicine* 2011

Recent advances in the developments of new treatments for celiac disease, Lahdeaho, Lindfors, Airaksinen, Kaukinen & Maki, *Expert Opin Biol Ther* 2012





The Clinical Development Process

- Compounds/medicines are created and tested in the lab
- Animal experiments are run to test safety
- Application is made to the U.S. Food and Drug Administration (FDA) for approval to test in humans
- Clinical trials are conducted to test safety and efficacy in humans
- Multiple clinical trials are conducted at different phases:
 - Phase 1, Phase 2, and Phase 3
- Application is made to the FDA for approval to market the drug





What is a clinical trial?

- Clinical trials are supervised research of new experimental medicines in humans prior to release of the medicine to the general public
- Clinical trials are conducted in various settings such as clinical research units, doctor's offices, and hospitals





Clinical Trial Phases – What do they mean?

- Clinical trials are conducted in a series of steps, called phases—each phase is designed to answer a separate research question
 - **Phase 1:** Researchers test a new drug or treatment in a small group of people for the first time to evaluate its **safety**, determine a safe dosage range, and identify side effects
 - **Phase 2:** The drug or treatment is given to a larger group of people to see if it is **effective** and to further evaluate its safety
 - **Phase 3:** The drug or treatment is given to large groups of people to **confirm** its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely



What happens in a clinical trial?

- Contact site recruiting for a specific trial
- Understand and agree to be in the trial
- Attend a screening visit, sign an informed consent form
- Comply with scheduled visits and procedures
- Report any adverse effects you notice while in the trial
- Complete an end-of-study visit





Potential Risks from Being in a Clinical Trial

- Your condition could get worse
- You may get placebo
- The experimental medicine may have side effects





Potential Benefits from Being in a Clinical Trial

- Your condition could improve
- You will have close contact to a medical team to evaluate your condition
- An opportunity to test a new medicine and contribute to humankind





Clinical Research Lingo

- **Protocol**

- Describes the way a study will be carried out
- Includes eligibility criteria, tests/procedures and medications used, risks, goals, and the length of the study

- **Double-Blind Study**

- Study where neither participants nor researchers know which group the participants are assigned
- Eliminates risk of bias by participants and researchers

- **Placebo**

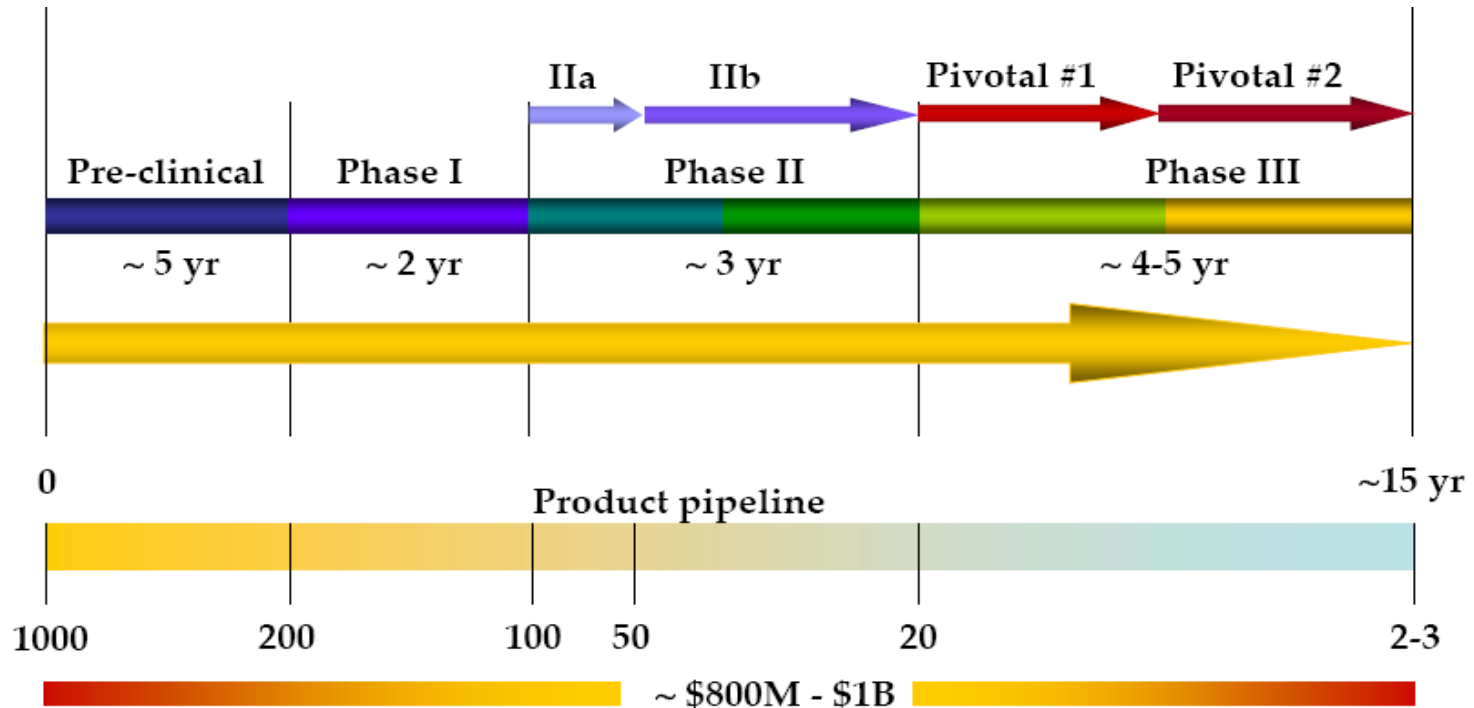
- An inactive pill or substance that is believed not to affect the disease being studied

- **Randomization**

- Process by which participants are assigned to treatment groups by chance
- Make each group as balanced as possible



Phases of Clinical Development





Clinical Trials in Celiac Disease

INVESTIGATIONAL AGENT	PHASE OF TRIALS	INVESTIGATOR-COMPANY COUNTRY	MECHANISM OF ACTION	ROUTE OF ADMINISTRATION	FINDINGS	SAFETY AND TOLERABILITY
Larazotide acetate (AT-1001)	2b	Alba Therapeutics, USA	Prevents opening of intestinal epithelial tight junctions	Oral	Ameliorated anti-tTG and symptom development in gluten challenges	Comparable to placebo
ALV003	2a	Alvine Pharmaceuticals, USA	Combination of two different gluten degrading proteases	Oral	Reduction in mucosal damage and immunologic activation	Comparable to placebo
AN-PEP	2a	DSM, Holland	Prolyl-endoprotease derived from <i>Aspergillus niger</i>	Oral	Reduction in intestinal deposits of anti-tTG IgA antibodies.	Comparable to placebo
NEXVAX2	1	NEXPep, ImmuSanT, Australia/USA	Desensitizing vaccine with 3 gluten peptides	SC injection	Development of IFN-gamma-producing anti gluten T-cells	Gastrointestinal Symptoms
NECATOR AMERICANUS	2a	Princess Adelaide University, Australia	Inhibits Th1 immune response by inducing a Th2 response	Skin incision	Better tolerance and reduced symptoms in gluten challenges	Active infection with helminth
Traficet-EN® (CCX282B)	2a	ChemoCentryx, Glaxo-Smith-Kline, USA	Inhibits CCR9, a chemokine receptor for gut T cell homing	Oral	Limits migration of T cells from the blood flow to the intestinal mucosa	Not reported

Non-dietary therapeutic clinical trials in coeliac disease

Laura Crespo Pérez, Gemma Castillejo de Villasante, Ana Cano Ruiz, Francisco León

European Journal of Internal Medicine 2011

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Questions?





NFCA Resources

- New web section: *Drug Development and Clinical Trials*
www.CeliacCentral.org/drugdevelopment
- Downloadables:
 - [Potential Pharmaceutical Treatments for Celiac Disease: An Interview with Joseph Murray, MD](#)
 - [Celiac Disease & Nexvax2 Fact Sheet](#)
- Video:
 - [Larazotide Acetate and Celiac Disease \(featuring Dr. Joseph Murray of the Mayo Clinic\)](#)
- Press release:
 - [Abbvie and Alvine to Collaborate on Investigational Oral Therapy for Celiac Disease](#)





More Resources

- Op-Ed by Alice Bast: [“Do You Know How Celiac Disease Works?”](#)
- www.FDA.gov
- www.ClinicalTrials.gov
- [FDA Drug Approval Process - PDF](#)





Save the Dates!

- **Topic:** *"Shifting the Focus: Lessons Learned from the Physical & Emotional Well-Being of Gluten-Free Athletes"*
- **Date:** Thursday, July 18, 2013
- **Time:** 2 p.m. Eastern/11 a.m. Pacific
- **Speaker:** **Dr. KC Wilder**, Sports Performance Coach

- **Topic:** *"GREAT U Special: Navigating the Gluten-Free Social Scene at College"*
- **Date:** Wednesday, August 7, 2013
- **Time:** 8:30 p.m. Eastern/5:30 p.m. Pacific
- **Speakers:** **Rebecca Panzer, MA, RD, LDN** and **Sam Master**, a third-year medical student living with celiac disease

- **Topic:** *"Kids Central Special: Packing the Gluten-Free School Lunchbox"*
- **Date:** Thursday, October 3, 2013
- **Time:** 8:30 p.m. Eastern/5:30 p.m. Pacific
- **Speaker:** **Garrett Berdan, RD, Chef**



Thank you!

- NFCA Contact: webinars@celiaccentral.org

