What's Taking So Long A Look into the Future

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Disclosures

- I have no financial affiliation with any product to be discussed during this presentation

Objectives

- Discuss the stages of drug development
- Discuss the process of getting a new drug to the market
- Discuss the cost of developing a new drug
- Discuss some of the current drugs in development

Drug Development Process

- Step 1
  - Discovery and development
- Step 2
  - Preclinical research
- Step 3
  - Clinical research
- Step 4
  - FDA review
- Step 5
  - FDA Post-Market safety monitoring

Discovery

- Typically, researchers discover new drugs through:
- New insights into a disease process that allow researchers to design a product to stop or reverse the effects of the disease.
- Many tests of molecular compounds to find possible beneficial effects against any of a large number of diseases.
- Existing treatments or drugs being researched that have unanticipated effects.
  - Viagra
- New technologies, such as those that provide new ways to target medical products to specific sites within the body or to manipulate genetic material.
- At this stage in the process, thousands of compounds may be potential candidates for development as a medical treatment. After early testing, however, only a small number of compounds look promising and call for further study.

Development

- Once researchers identify a promising compound for development, they conduct experiments to gather information on:
- How it is absorbed, distributed, metabolized, and excreted.
- Its potential benefits and mechanisms of action.
- The best dosage.
- The best way to give the drug (such as by mouth or injection).
- Side effects or adverse events that can often be referred to as toxicity.
- How it affects different groups of people (such as by gender, race, or ethnicity) differently.
- How it interacts with other drugs and treatments.
- Its effectiveness as compared with similar drugs.

Preclinical Research

- Before testing a drug in people, researchers must find out whether it has the potential to cause serious harm, also called toxicity. The two types of preclinical research are:
- In Vitro-Latin for “within the glass.” When something is performed in vitro, it happens outside of a living organism
- In Vivo-Latin for “within the living.” It refers to work that’s performed in a whole, living organism.
- FDA requires researchers to use good laboratory practices (GLP), defined in medical product development regulations, for preclinical laboratory studies. These regulations set the minimum basic requirements for:
  - study conduct
  - personnel
  - facilities
  - equipment
  - written protocols
  - operating procedures
  - study reports
  - and a system of quality assurance oversight for each study to help assure the safety of FDA-regulated product
- Usually, preclinical studies are not very large. However, these studies must provide detailed information on dosing and toxicity levels. After preclinical testing, researchers review their findings and decide whether the drug should be tested in people.

Phase	Primary Goal	Dose	Patient Monitor	Typical Number of Participants	Number of Participants Note
Phase 0	Pharmacokinetics particularly oral bioavailability and half-life of the drug	Very small, sub-therapeutic	Clinical researcher	10 people	Often skipped for phase 1

Phase	Primary Goal	Dose	Patient Monitor	Typical Number of Participants	Number of Participants Note
Preclinical	Testing of drug in non-human subjects, to gather efficacy, toxicity and pharmacokinetic information	Unrestricted	A graduate level researcher (PhD)	Not applicable- In vitro and in vivo only	

Clinical Research

- While preclinical research answers basic questions about a drug's safety, it is not a substitute for studies of ways the drug will interact with the human body.
- "Clinical research" refers to studies, or trials, that are done in people.
- As the developers design the clinical study, they will consider what they want to accomplish for each of the different Clinical Research Phases and begin the Investigational New Drug Process (IND), a process they must go through before clinical research begins.

- This is where the 4 clinical phases are located

Phase I

Phase	Primary Goal	Dose	Patient Monitor	Typical Number of Participants	Number of Participants Note
Phase I	Testing of drug on healthy volunteers for dose-ranging	Often subtherapeutic but with ascending doses	Clinical researcher	20-100 Length of study is several months About 70% move on to next phase	Determines whether drug is safe to check for efficacy

Phase II

Phase	Primary Goal	Dose	Patient Monitor	Typical Number of Participants	Number of Participants Note
Phase II	Testing of drug on patients to assess efficacy and safety	Therapeutic dose	Clinical researcher	100-300 Length of study is several months to 2 years About 33% move on to next phase	Determines whether drug can have any efficacy; at this point, the drug is not presumed to have any therapeutic effect whatsoever

Phase III

Phase	Primary Goal	Dose	Patient Monitor	Typical Number of Participants	Number of Participants Note
Phase III	Testing of drug on patients to assess efficacy, effectiveness and safety	Therapeutic dose	Clinical researcher and personal physician	300-3000 Length of study is 1-4 years About 25-30% move on to the next phase	Determines a drug's therapeutic effect; at this point, the drug is presumed to have some effect

FDA Recommendations
Celiac Disease

- Pharmacological trials for the treatment of CD, prevention of histological damage should be a major endpoint in Phase 2 studies

- Improvement of CD related patient-reported outcomes and QOL should both be the primary end points in Phase 3 studies

FDA Review and Step 5 Post-Marketing Surveillance

Phase	Primary Goal	Dose	Patient Monitor	Typical Number of Participants	Number of Participants Note
Phase IV	Postmarketing surveillance – watching drug use in public	Therapeutic dose	Personal physician	Anyone seeking treatment from their physician who has the disease Typically lasts for the life of the drugs	Watch drug's long-term effect Continue to monitor safety and efficacy

What Does It Cost To Get A Drug To The Consumer

- The average cost is between $2-$3 billion
- Anti-cancer drugs up to $4.54 billion
- Considering ONLY the clinical trial portion, it depends on the disease and it ranges from $2 million up to $347 million. The average was $19 million
  - Trials using 100 patients or less averaged just $6 million
  - Trials using 1000 patients or more averaged $77 million for cardiac studies and $21 million for endocrine/metabolic diseases

Drug Patent

- Patents are good for only 20 years
- Clock starts when the patent application is filed
- It could take 8 years for the drug to reach the general public
- Once the patent expires and generics start hitting the market, brand sales can dop by 80%
- Patents can be extended by up to 5 years
- Due to the rigorous amount of testing that goes into obtaining a drug patent, many larger drug companies file multiple patent applications in order to extend that 20 year deadline
- Patents can also be extended if the company want to market it later for use in pediatrics

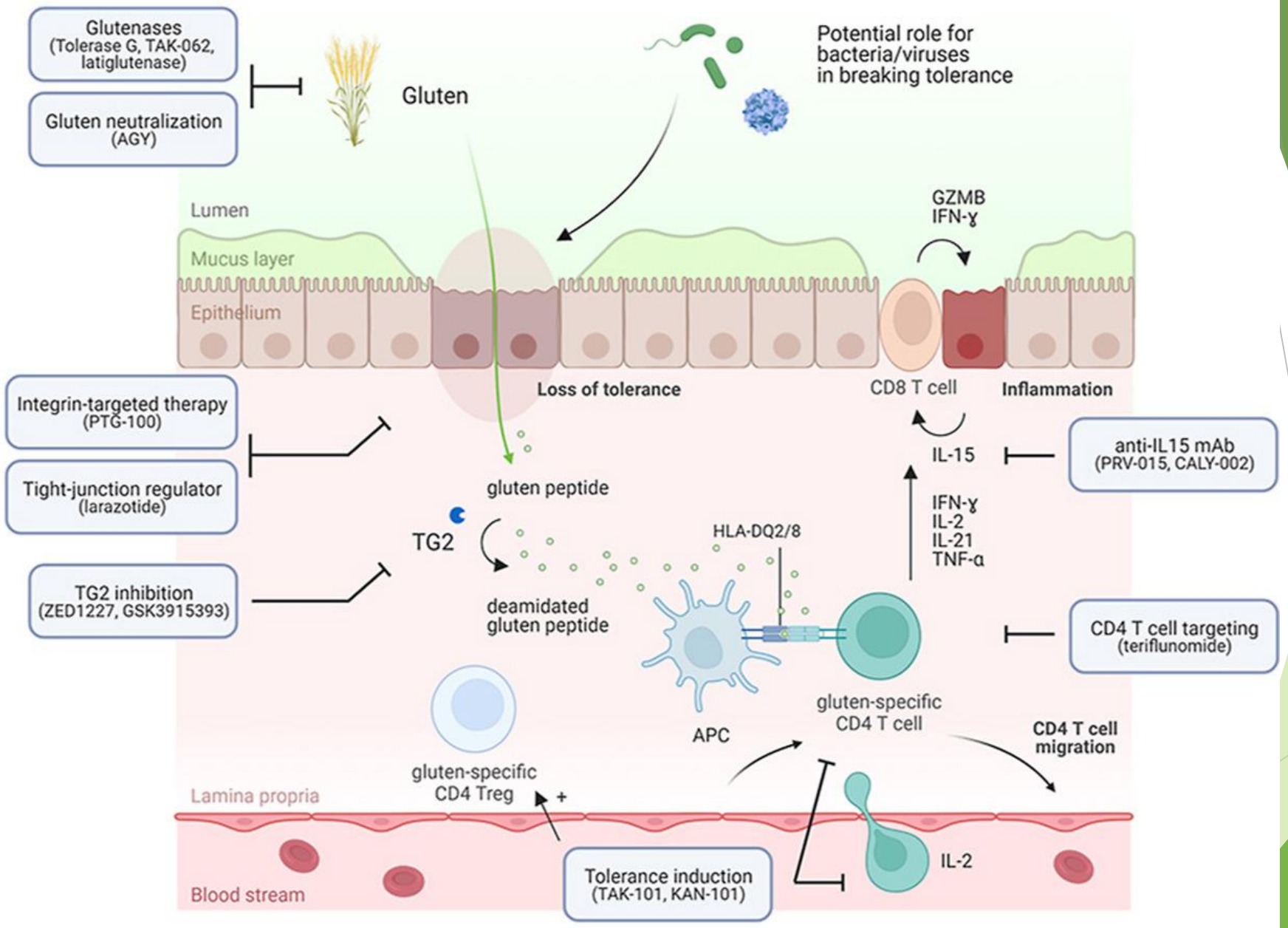
Expedited Drug Development

The **FDA** has developed several programs to expedite drug development and review for therapies addressing serious conditions and unmet medical needs. These programs include:

- Fast Tract Designation: Facilitates the development and review of drugs for serious or life-threatening conditions, aiming to fill unmet medical needs.
- Breakthrough Therapy Designation: Accelerates the evaluation of drugs showing substantial improvement over existing treatments.
- Accelerated Approval: Allows conditional approval based on surrogate endpoints, with post-marketing studies required for full approval.
  - Surrogate endpoint is part of a composite of biomarkers
  - Ex: decrease in tTG levels, vaccine antibodies
- Priority Review Designation: Speeds up the review process for drugs that offer significant benefit over existing options

Drug Strategies to Treat Celiac Disease

- Blocking Immunogenic Gluten Exposure
- Transglutaminase Inhibition
- Immune Modulation
- Inducing Immune Tolerance


Glutenases
(Tolerase G, TAK-062, latiglutenase)
Gluten neutralization
(AGY)
Gluten
Potential role for bacteria/viruses in breaking tolerance
Lumen
Mucus layer
Epithelium
GZMB
IFN-ɣ
Loss of tolerance
CD8 T cell
Inflammation
Integrin-targeted therapy
(PTG-100)
Tight-junction regulator
(larazotide)
TG2 inhibition
(ZED1227, GSK3915393)
gluten peptide
TG2
deamidated gluten peptide
HLA-DQ2/8
IL-15
anti-IL15 mAb
(PRV-015, CALY-002)
IFN-ɣ
IL-2
IL-21
TNF-α
CD4 T cell targeting
(teriflunomide)
APC
gluten-specific CD4 T cell
CD4 T cell migration
gluten-specific CD4 Treg
+
Lamina propria
Tolerance induction
(TAK-101, KAN-101)
IL-2
Blood stream

Drug Name (Developer)	Most Recent Study Phase	Potential Relevant Intellectual Property (IP)	Relevant Business Information
Gluten Modification/Neutralisation			
Latiglutenase, formerly IMGX-003 or ALV-003 (Entero Therapeutics, formerly ImmunogenX)	Phase 2b (oral, dissolvable powder) (NCT04243551) active, not recruiting PCD: 12/2023	WO2008/115411 (combination enzyme therapy) WO2010/021752 (oral formulation)	Originator Stanford (Chaitan Khosla lab), founding Alvine Pharmaceuticals and non-profit Celiac Sprue Research Foundation 07/2013: ImmunogenX founded 12/2023: combination with First Wave BioPharma: "initiation of Phase 3 trials expected in 2H/2024" 05/2024: company name changed to Entero Therapeutics
Zamaglutenase, also TAK-062 or Kuma062 (Takeda Pharmaceuticals)	Phase 2 (oral, tablet) (NCT05353985) active, not recruiting PCD: 05/2025	WO2016/200880 (composition of matter) WO2022/094177 (composition of matter)	02/2020: Takeda exercised option to purchase PvP Biologics, which was founded in 2012 by the originators from University of Washington
AN-PEP, or GliadinX® (Dr. C. Bonorino Udaondo Gastro-enterology Hospital, Argentina)	Phase 4 (oral, capsule) (NCT04788797) completed PCD: 07/2022	No IP found	Marketed as medical device e.g. GliadinX®, Tolerase® G or GluteZym®
AGY-010 (IGY Life Sciences, Vetanda Group)	Phase 2 (oral, capsule) (NCT03707730) completed PCD: 12/2023	WO2005/099753 (method of use)	10/2019: last update on clinicaltrials.gov 07/2022: reported to produce nutraceutical IgY ingredient in 94.8% purity from hen egg yolks
Transglutaminase 2 Inhibition			
ZED1227/TAK-227 (Takeda Pharmaceuticals)	Phase 2b (oral, capsule) (EudraCT 2020-004612-97) ongoing started: 08/2021	WO2014/012858 (composition of matter) WO2021/214337 (new oral formulation)	Originally discovered by Zedira 2011: EP rights licensed to Dr. Falk Pharma 10/2022: Takeda entered in a collaboration and licensing agreement with Zedira and Dr. Falk Pharma
GSK3915393 (GlaxoSmithKline)	Phase 1 (oral, capsule) (NCT04604795) completed PCD: 06/2021	WO2020/033784 (composition of matter)	09/2019: GSK gained rights by Sitari Pharmaceuticals aquisition 02/2023: CelD development stopped, however Phase 2 started in idiopathic pulmonary fibrosis
Tolerance Inducing Strategies			
TAK-101, formerly CNP-101 or TIMP-GLIA (Takeda Pharmaceuticals)	Phase 2 (iv infusion) (NCT04530123) recruiting PCD: 10/2025	WO2017/143346 (pharmaceutical composition)	10/2019: Takeda acquired the license from Cour Pharmaceuticals
TPM502 (Topas Therapeutics)	Phase 2a (iv infusion) (NCT05660109) recruiting PCD: 05/2024	WO2021/165227 (composition of matter) WO2022/253950 (composition of matter)	In-house development since foundation in 2016
KAN-101 (Anokion)	Phase 1b/2 (NCT05574010) recruiting PCD: 12/2024 Phase 2a (iv infusion) (NCT06001177) recruiting PCD: 03/2025	WO2015/140648 (composition of matter) WO2021/053589 (composition of matter)	09/2019: Anokion acquired Kanyos Bio, adding KAN-101 to the portfolio 10/2022: Pfizer made $35 million equity investment in Anokion. Pfizer and Anokion entered a partnership to support the development of KAN-101 05/2023: Fast Track Designation granted by FDA

Drug Name (Developer)	Most Recent Study Phase	Potential Relevant Intellectual Property (IP)	Relevant Business Information
Immunomodulating Strategies			
IL-15 Targeting			
Ordesekimab PRV-015/AMG 714 (Amgen/Provention Bio)	Phase 2b (sc injection) (NCT04424927) active, not recruiting PCD: 08/2024	WO2017/217985 (method of use) WO2004/076620 (composition of matter)	Developed by Amgen in collaboration with Provention Bio, a Sanofi company; originally from Genmab
CALY-002 (Calypso Biotech)	Phase 1b (iv infusion) (NCT04593251) completed PCD: 04/2024	WO2016/001275	02/2013: spin-off from Merck Serono (licenced from iDD Biotech) 01/2024: company aquired by Novartis
TEV-53408 (Teva)	Phase 1 (sc injection) ongoing	No IP found	In-house development since 2019
EQ102, formerly BNZ-2 (Equillium Bio)	Phase 1 (sc injection) ongoing	WO2017/062685 WO2018/187499	02/2022: obtained via Bioniz Therapeutics acquisition 12/2023: bioavailability lower than expected; switched to EQ302 with superior product profile (planned Phase 1 study in 2H 2025)
Inhibition of T-Cell Activation			
DONQ52 (Chugai Pharmaceutical/ Roche)	Phase 1 (sc injection) (NCT05425446) active, not recruiting PCD: 05/2024	WO2018/155692 (antibody and its use for the treatment of CelD) WO2020/204054	In-house monoclonal antibody development from Chugai Pharmaceutical
Lymphocyte Trafficking			
PTG-100 (Protagonist Therapeutics)	Phase 1b (oral, capsule) (NCT04524221) completed PCD: 04/2022	WO2014/059213 WO2015/176035 WO2016/054411 (composition of matter for peptidic α4β7 integrin antagonist)	Originator: Stanford University (Prof. Nielsen Fernandez-Becker)
JAK Inhibition			
Ritlecitinib (Pfizer)	Phase 2 (oral, capsule) (NCT05636293) recruiting PCD: 08/2025	WO2015/083028 (composition of matter) WO2020/084435 (tosylate salt)	Massachusetts General Hospital (Prof. Alessio Fasano)
Tofacitinib (Pfizer)	Phase 2 (oral, tablet) (Eudra CT: 2018-001678) completed started: 06/2019	No medical use patent for CelD found (composition of matter lapsed)	Investigator-initiated clinical trial from VU Medical Center, Amsterdam (Prof. Frits Koning)
Barrier Function and Integrity			
Tight Junction Modulation			
Larazotide actetate (9 Meters Biopharma)	Phase 3 (oral, capsule) (NCT03569007) terminated by sponsor PCD: 07/2022	WO2021/034629 (formulation) WO2000/007609 (lapsed) (composition of matter)	07/2023: ceased operations (available for licensing)
Intestinal Epithelial Regeneration			
IMU-856 (Immunic)	Phase 1/1b (oral, tablet) completed	WO2019/054427 (composition of matter)	11/2018: inlicensed from Daiichi Sankyo

Oral Products On The Market

- Gliadin X
- Gluten Digest
- Gluten Rid
- Gluten Cutter
- And others
- There's no good evidence that the enzymes currently on the market can protect people with celiac disease from even small amounts of gluten
- They do not replace a GFD
- They provide a false sense of security

AN-PEP

- Uses the active enzyme in Gliadin X
- Dietary supplement which breaks down gluten in the stomach
- Given orally
- Problem: can only detoxify 0.20-0.50 g of gluten
  - Equal to 1/8-1/4 slice of bread
- Drug study goal-reduce gluten by 50%
  - Only achieved in 10/13 volunteers
- Should only be used in conjunction with GFD for accidental contamination

Breaking Down Gluten Using Enzymes

- E40 (Nemysis)
  - Mid preclinical stage
- Latinglutenase (IMGX-003)
  - About to enter Phase 3
- Zamaglutenase (TAK-062)
  - Starting Phase 2
- AGY-010
  - Phase 2

E40
Pre-Clinical Phase

- Oral product
- Breaks down gluten in the stomach
  - No immunological fragments left to enter the intestine
  - It breaks down all 6 of the immunological parts of the antigen that is recognized by the patient's immune system
- Produced through recombinant technology
- Resistant to acid breakdown in the stomach
- Maintains 50% of its activity in the small intestine
- Because it is in the Preclinical phase, dose and frequency not yet known

Latiglutenase (IMGX003)

- Phase 2b, BUT
- The Phase 3 clinical development plan for latiglutenase has been reviewed by the FDA
  - Should commence very soon (second half 2024)
  - Target is to enter market 2027
  - Previously known as ALV003
- Administered orally
- Taken with meals
- Meant to break down gluten in the stomach

Larazotide Failure

- Similar to Latiglutenase
- Was set to start Phase 3
- Mechanism was to decrease intestinal permeability and regulate the tight junction between intestinal cells (ie, Zonulin gate)
- Planned for 525 patients
- Mathematical modelling determined a much larger patient population needed
- Company could not afford the additional funds needed

Zamaglutenase (TAK-062)

- Phase 2
- Endopeptidase
- Drug given orally
  - Currently studying as a liquid, tablet, and capsule forms
- Stated to degrade 99% of gluten within 10 minutes
  - Dose up to 900 mg of drug
  - Up to 9 g gluten was given
- Take home point
  - 1 slice of bread = ~5 g gluten
  - 99% efficacy = 50 mg gluten
  - Threshold = ~10-50 mg gluten

Food Item	Calculated Gluten (g)	Analyzed Gluten (g)	Gluten as a Percentage of Total protein (%)
All Bran Flakes ®	9.41	0.109	0.9
*All Purpose Flour	10.67	44.82	336
Chicken Noodle Soup	0.96	0.5178	43
Chocolate Chip Cookies	2.7586	2.3817	70
Couscous	9.68	1.1531	9
Dry Penne Pasta	8.89	1.9696	18
*Egg Quesadilla	2.97	3.8244	102
Fish Sticks	2.24	0.6773	24
Lean Cuisine Chicken/Pasta Frozen Dinner ®	1.49	0.716	38
*Mini Muffin	3.478	4.5667	105
Mini Ravioli	1.887	1.6562	72
Multigrain Bagel	8.727	5.6472	52
Nutrigrain Bar ®	4.324	1.3303	25
Orzo Pasta	10.353	0.7013	5
Pizza Pops ™	4.8	3.4085	57
Pot Barley	20	20.565	82
**Quick Oats	10	0.005	0.0004
*Rye Bread	5.33	13.77	206
*Rye Flour	9.1429	26.591	233
Shreddies ®	6.4	4.5022	56
Spelt Bread	6.956	5.6007	64
Vegetable Barley Soup	0.64	0.7915	99
Wheat Crackers	8.4	6.5077	62
*White Bread	6.76	14.883	176
*Whole Grain Bread	8.89	29.704	267

**Quick Oats < 5 ppm
*Analyzed gluten> 100% of total protein
Table 1: Food Items studied with Calculated and Analyzed Gluten content per 100 g; and analysed gluten expressed as a percentage of Total protein per 100 g food items

AGY-010

- Phase 2
- Administered orally
  - To prevent the recurrence of symptoms in persons with CD
- Drug derived from egg yolk (egg allergy beware!!!!)
- Works as an anti-gliadin antibody
- Anti-gluten immunoglobulin yolk antibodies bind to problematic wheat proteins, making them harmless to those with celiac disease
- Initially meant to prevent effects of accidental exposure

Interrupting The Immediate Or Delayed Effects Of Gluten On The Cells Lining The Intestine

- IMU-856
  - Phase 2 to begin

IMU-856

- End of Phase 1
- Oral delivery
  - Current dosing-daily administration
- New approach to restore intestinal barrier function by regenerating bowel epithelial tissue without affected overall immune system

Preventing The Enzyme tTG From Modifying Gluten In The Cell

- This helps reduce the abnormal immune response
- Zed1227/TAK227

ZED1227

- Transglutaminase 2 blocker
- Transglutamidase
  - Deamidates dietary gluten
  - This results in the production of the antigen responsible for the strong anti-gluten T-cell reaction
- Blocks the immune reaction caused by gluten
- Effectively prevented gluten-induced intestinal mucosal damage and inflammation
- Of important note, the genes responsible for absorption of nutrients and trance elements were returned to normal
- Given orally 100 mg/day

Inducing Immune Tolerance To Protect Against The Effects of Gluten By Preventing An Immune Reaction

- TAK-101
  - Phase 2
- TMP502
  - Phase 2
- KAN101
  - Start Phase 2
- AG017
  - Phase 1b/2a
- ALL-001
  - Mid preclinical stage
- SQZ TAC
  - Mid preclinical stage

TAK-101

- Phase 2a
- Given intravenously
- Prevents gluten from triggering an immune reaction
  - Carries a hidden component of gluten to reprogram the immune system not to react

TPM502

- Phase 2a
- Goal is to study immune tolerance. They are also studying depression of symptom severity in response to gluten exposure
- Doses are administered by infusion only at this time

KAN-101

- Phase 2a
- Injectable doses
- Gluten antigen is delivered to the liver
- Targets the immune cells. Aims to restore immune tolerance to gluten
  - Re-teaches the immune system not to respond to the immunological effects of gluten
  - Unlike broad immunosuppressants, it only targets the part of the immune system that drives celiac disease

AG017

- Phase 1b/2a
- Filed with FDA for IND
- Given orally
- Antigen specific with potential to reverse gluten sensitivity

ALL-001

- Preclinical stage
- Aims to modulate the immune system's response to gluten
  - Interferes with the immunological cascade of events triggered by gluten exposure
- Hope is to allow someone with CD to eat gluten without the causing an immune response

SQZ TAK

- Mid preclinical stage
- Aims to delete antigen specific T-cells to improve tolerance after a gluten exposure
  - Doesn’t cause broad immune suppression

Amlitelimab (KY1005)

- Phase 2a/b
- Non T-cell depleting monoclonal antibody
  - Immune regulator
- Administered SubQ (every 12 weeks?)
- Target group-those non-responsive already on a GFD
- Originally developed to treat atopic dermatitis

Interrupting The Immune Reactions That Occur

- PRV-015 (Prev AMG714)
  - Mid Phase 2
- CALY-002
  - Mid Phase 1
- Hu-Mik-Beta 1
  - End Phase 1
- EQ-302
  - End Pre-Clinical
- DONQ52
  - Start Phase 1
- TAK-101
  - Phase 2

PRV015

- Phase 2b
- Monoclonal antibody works by blocking cytokine production
  - Cytokines
    - are produced by the immune system
    - released with gluten consumption
    - create inflammation and small intestinal damage
    - prominent cytokine is interleukin-15 (IL-15)

CALY-002

- Phase 1b
- IL-15 specific monoclonal antibody
  - Monoclonal antibodies are man-made proteins that bind to substances in the body
  - In autoimmune diseases (such as CD), the antibodies are designed to target cytokine proteins that contribute to inflammation

HU-MIK-Beta-1

- Objective is to see if antibody therapy is a safe and effective treatment for CD that has not responded to other treatments (refractory CD)
- Three doses given by injection 3 weeks apart

EQ-302

- Selective inhibitor of IL-15 and IL-21
  - Increased levels result in increased inflammation and villous atrophy
  - Pre-Clinical stage
  - Oral administration
  - Replaces EQ-102 which showed limited bioavailability in Phase 2

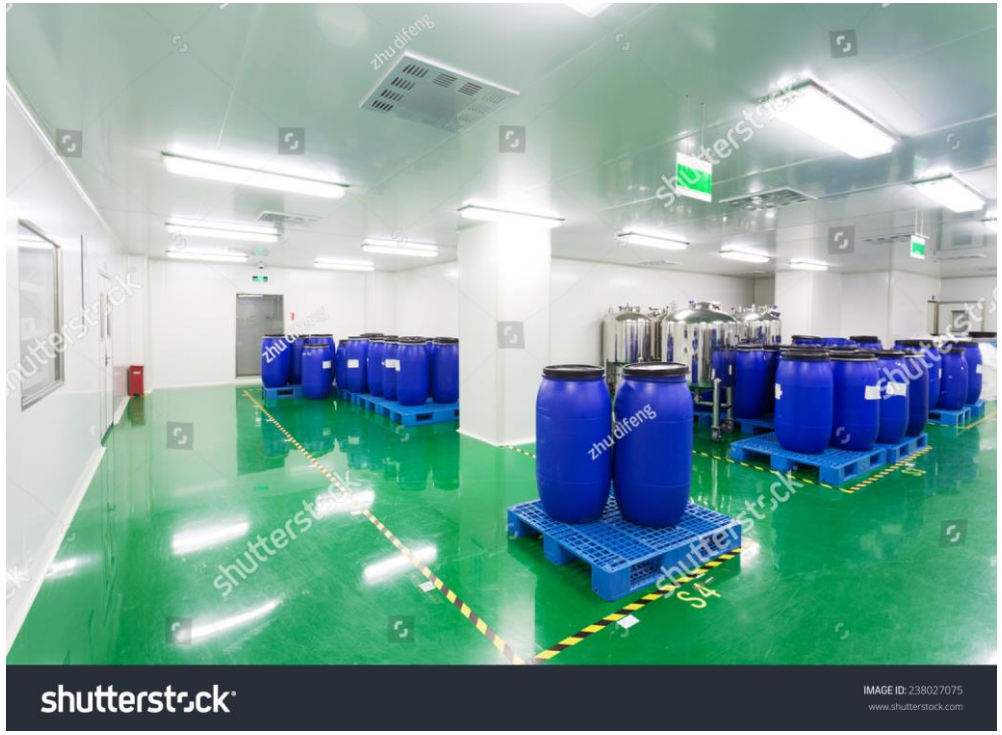
DONQ2

- Phase 1
- Multispecific anti-gluten antibody (HLA DQ2.5)
  - Selectively and broadly recognize more than 25 distinct pathogenic gluten pHLA-DQ2.5, and directly neutralize gluten dependent T-cell activation.
  - Selectively inhibits the immune response to gluten in CD
    - Blocks immunity to gluten w/o affecting systemic immunity
- Since it's a Phase 1 study, oral vs IV unknown
- Results of the study so far is that DONQ52 is highly effective at blocking gluten-specific T cell responses to dominant wheat gluten epitopes
  - Studies on barley and rye are underway

TAK-101

- Phase 2a
- Gluten protein (gliadin) encapsulated in a nanoparticle designed to induce gluten-specific tolerance
- Administered intravenously on days 1 and 8
- Mechanism regulate immune tolerance

Quality Control
Cross Contamination Risk Avoidance



Air filtration; FDA requires air to be filtered 20 times per hour: an operating room is filtered 15-25 times per hour

Quality Control
Cross Contamination Risk Avoidance

Dust Collection

Pill Production

Tablet Production Room

Continue to eat gluten free!!!

QUESTIONS??

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HOW ABOUT THE TUNA?
TOO MUCH MERCURY.
THE VEAL?
TOO CRUEL.
THE BEEF?
ONLY IF IT'S ORGANIC... TOO MANY HORMONES.
MAYBE THE MARINARA.
TOO... HEAVY.
I HEAR EGGS ARE BACK.
ONLY IF THE HENS ARE FREE-RANGE.
WHEN DID EATING BECOME SO COMPLICATED?
THANKS.
I GUESS YOU CAN'T GO WRONG WITH TOAST.
SHOOT! I MEANT TO ORDER GLUTEN-FREE.