AMG 714, an anti-IL-15 antibody in development for the treatment of Celiac Disease and Refractory Celiac Disease Type II

Francisco Leon, MD PhD
Disclosures

• Co-founder, former CEO/CMO, Celimmune LLC
  - Since end of 2017, a wholly owned subsidiary of Amgen Inc
  - Consultant, Amgen Inc

• Former CMO, Alba Therapeutics

• Partner, Biomedal SA

• Co-founder, director, Glutenostics LLC

• Co-founder, CSO, Provention Bio

• President, PharmImmune LLC
Celiac patients’ attitudes regarding novel therapies

CeD Pathogenesis and Therapeutic Targets

Schuppan, Gastroenterology 2009

Refractory celiac, in situ small bowel Tc lymphoma

Intestinal Mucosal Atrophy

Intestinal symptoms, nutritional complications

Anti-tTG
Experimental non-dietary therapies for celiac disease (2010)

**Alvine:** ALV-003

**Alba:** Larazotide acetate

**Chemocentryx:** Traficet EN

**ImmusanT:** NexVax2

**James Cook Univ:** Necator americanus

Schuppan
Gastroenterology
2009, modified
Experimental non-dietary therapies for celiac disease (2018)

**Universities:** Modified G

*Probiotics* – Ph2

**BiolineRx:** BL-7010 – Ph1

**Innovate:** – INN-202 - Ph2b (formerly Alba’s larazotide)

**Chicago Celiac Center:** Montelukast – Ph1b

**Zedira/Falk Pharma:** ZED1227 – Ph2a

**Sitari:** Pre-clinical tTG inhib (GSK)

**UCB:** Pre-clin tTG inhibitor

**Provid:** Pre-clinical

**Schuppan Gastroenterology 2009, modified**

**ImmunogenX:** Latiglutensase/IMGX-003 (formerly Alvine’s ALV-003)- Ph2b

**Allergan:** Viokase/pancrelipase – Ph2a

**PvP Biologics:** KumaMax Pre-clinical (Takeda)

**IGY Life Sciences:** IgY – Ph1/2

**Celimmune:** AMG 714 – Ph2a (Amgen)

**Mayo Clinic/NCI:** HuMikβ1 – Ph2a

**Calypso:** CALY 002 – Pre-clinical (Merck KGa)

**Bioniz:** BNZ-2 – Pre-clinical (Takeda)

**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
We need multiple shots on goal since: 1) most experimental medicines fail to be approved 2) it’s likely that combinations will be needed
IL-15 is a central regulator in celiac and refractory celiac disease


Loss of oral tolerance  
Loss of immune regulation  
Lymphokine killer activity  
Increased cell survival  
Epithelial cell destruction  
Lymphomagenesis
Interleukin 15-Dependent T Cell-like Innate Intraepithelial Lymphocytes Develop in the Intestine and Transform into Lymphomas in Celiac Disease

Graphical Abstract

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In Brief
Ettersperger, Montcuquet et al. showed that innate lymphocytes with T cell traits were present in the gut epithelium. The latter cells differentiated independently of Id2 in response to NOTCH and IL-15 signals. They acquired gain-of-function
AMG 714 efficacy in celiac models
AMG 714 induces apoptosis of IELs in Active Celiac and RCD II explants

Epithelial Damage
Lymphomagenesis
Survival & Clonal Expansion

IL-15
Dendritic cell
Gluten-specific CD4 T cell

Malamut et al. “IL-15 triggers an antiapoptotic pathway in human intraepithelial lymphocytes that is a potential new target in celiac disease–associated inflammation and lymphomagenesis.” J Clin Invest 2010
CELIM- NRCD-001: Gluten Challenge study of AMG 714 to test potential in GFD Non-Responsive Celiac Disease
Finland (Maki): Tampere (Lähdeaho), Turku (Scheinin), Oulu (Vuotikka)
Measuring gluten immunogenic peptides (GIP) facilitates the conduct of celiac clinical trials and helps self-monitoring of the GFD by patients.
CELIM-RCD-002: AMG 714 to treat RCD-II/Pre-EATL
San Diego (Crowe...), NYC (Green, Bhagat, Vlad...), Paris (Cellier, Cerf-Bensussan...), Amsterdam (Mulder, Bouma, Van Gils, Lundin, Sanders...), Tampere (Collin...), Madrid (Crespo...)
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