Will the treatment always be just a gluten free diet? What's on the horizon?

Ludvig M. Sollid

Wheat Field Under Threatening Skies van Gogh 1890

Coeliac UK Annual Research Conference

Coeliac disease; Potential to refractory and everything in between

March 20, 2020

Conflicts of interest

Privately or via employer been consultant during the two last years for:

ImmusanT Therapeutics
Interexon Actobiotics
Bioniz Therapeutics
UCB Biopharma
Chugai Pharmaceutical
Merck
GSK

Experimental non-dietary therapies for celiac disease (March/2020)

Universities: Modified Gluten

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ActoBio*: AG017* – Ph1/2

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(larazotide acetate)

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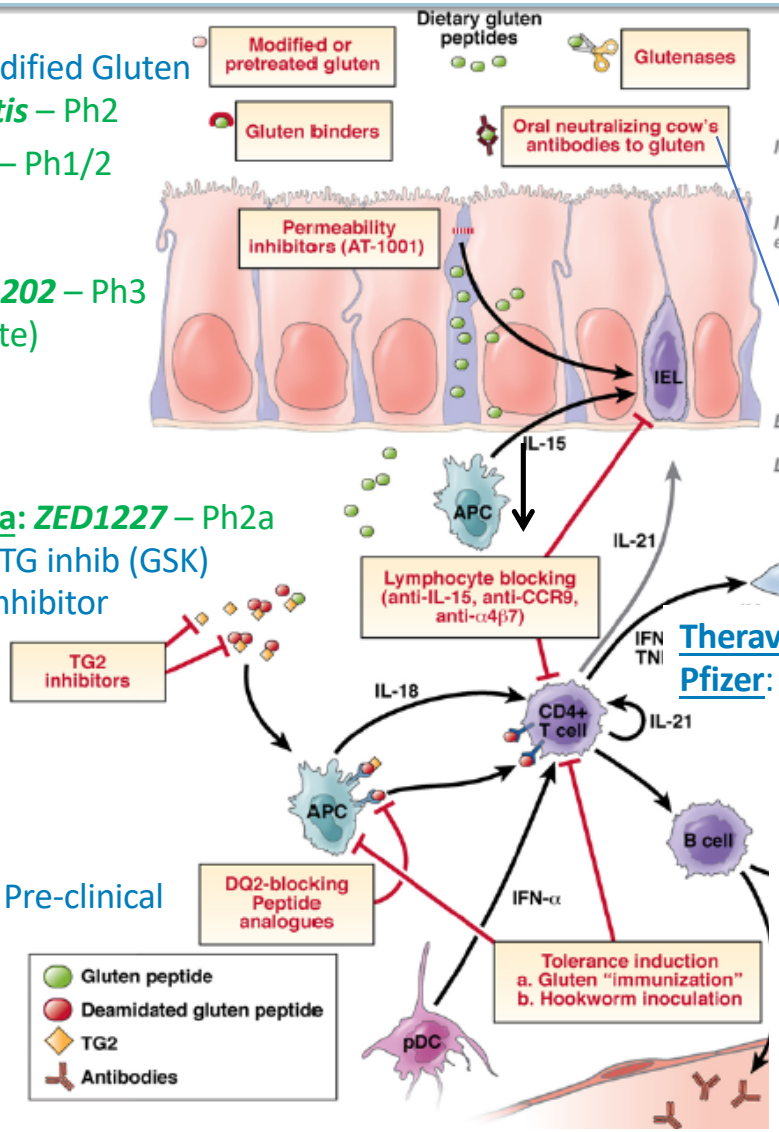

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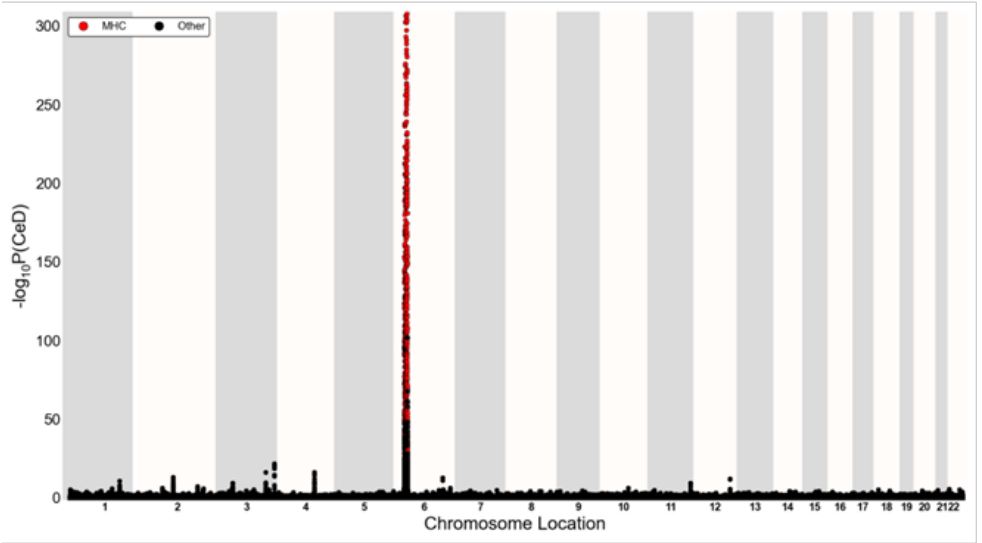
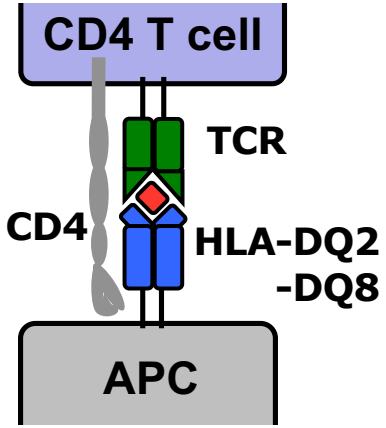
Allero: Pre-clinical

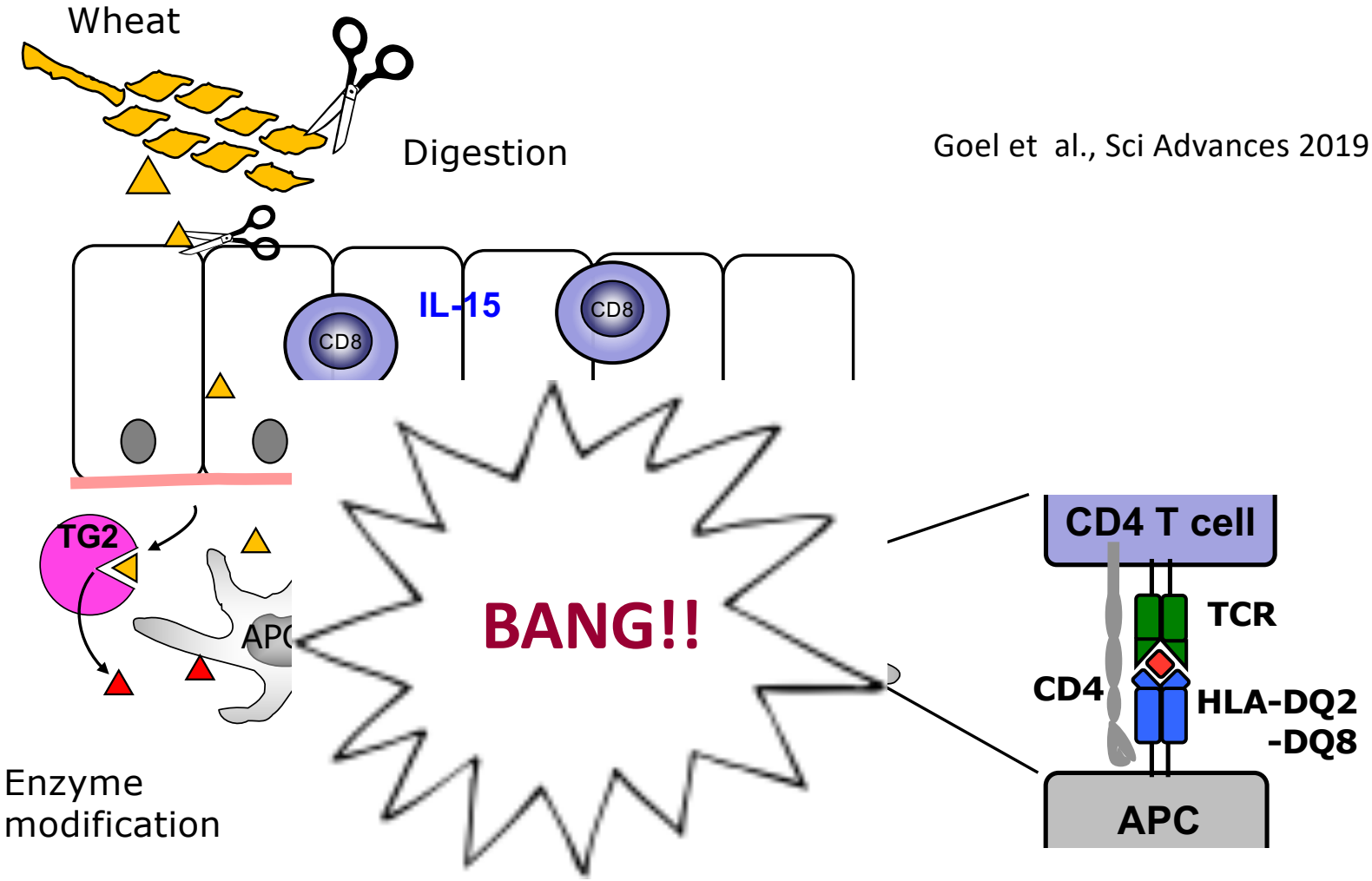
Fransisco Leon

GWAS Celiac disease – HLA!!





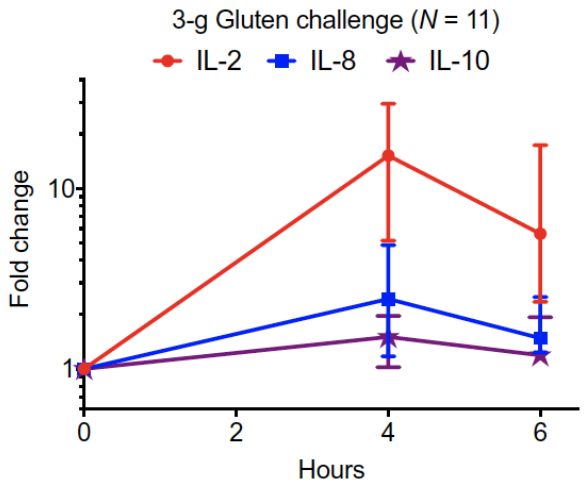
The coeliac lesion

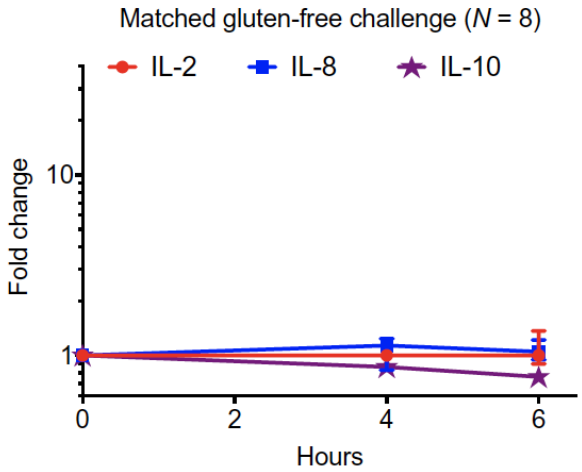


Goel et al., Sci Advances 2019

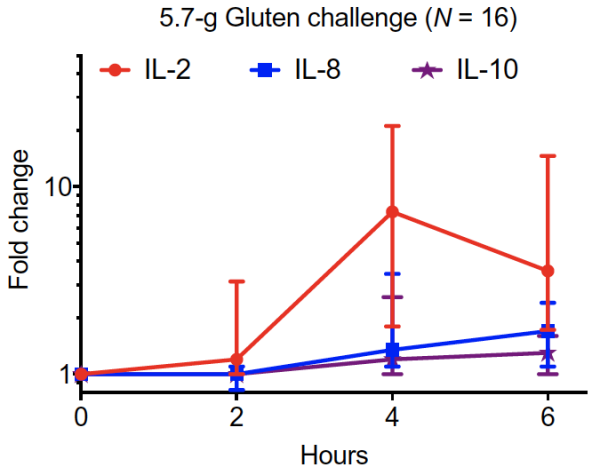
Serum/plasma cytokines increase shortly after oral gluten challenge

Australia



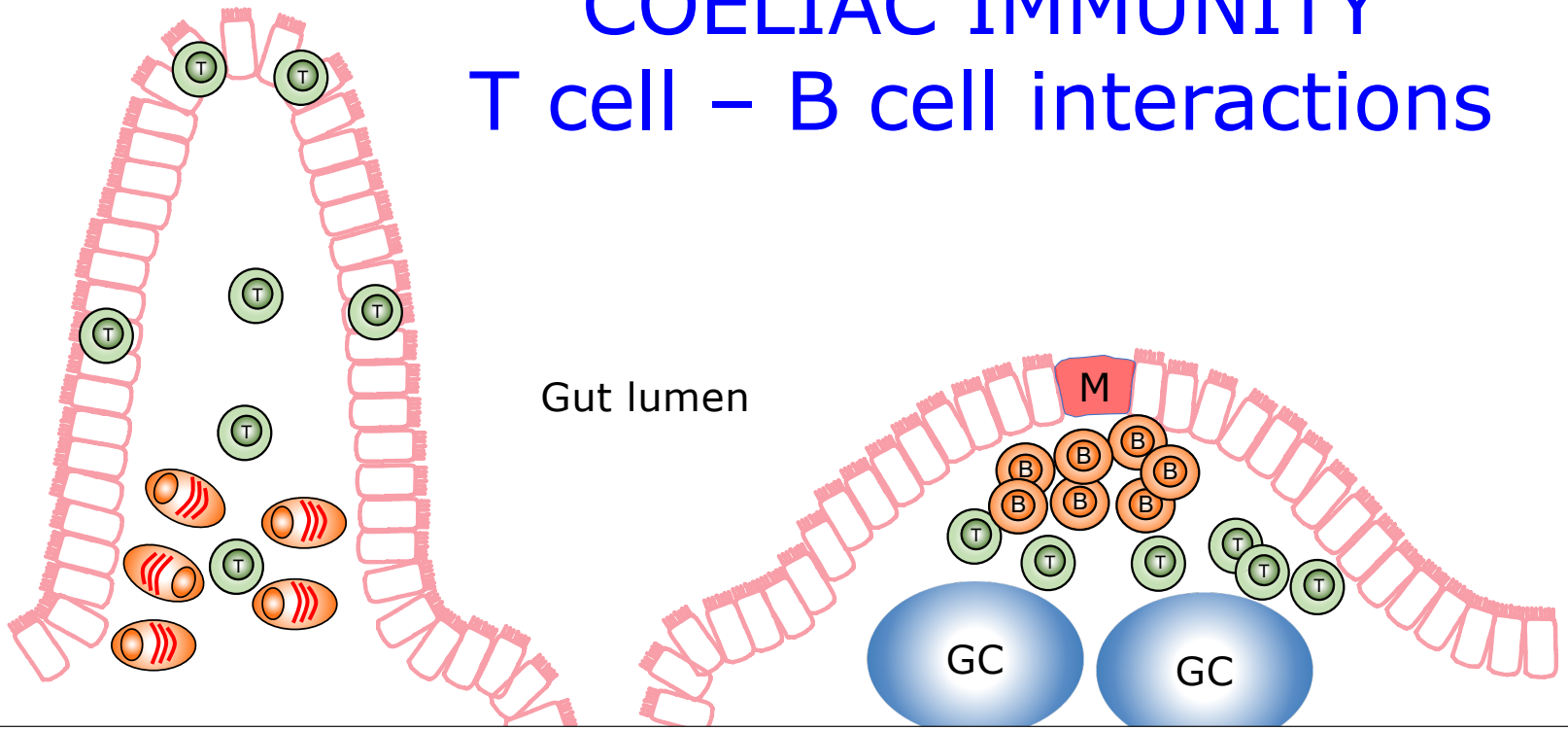


Norway



Goel et al., Sci Advances 2019

COELIAC IMMUNITY
T cell – B cell interactions



Effector sites

Lamina propria

Blood

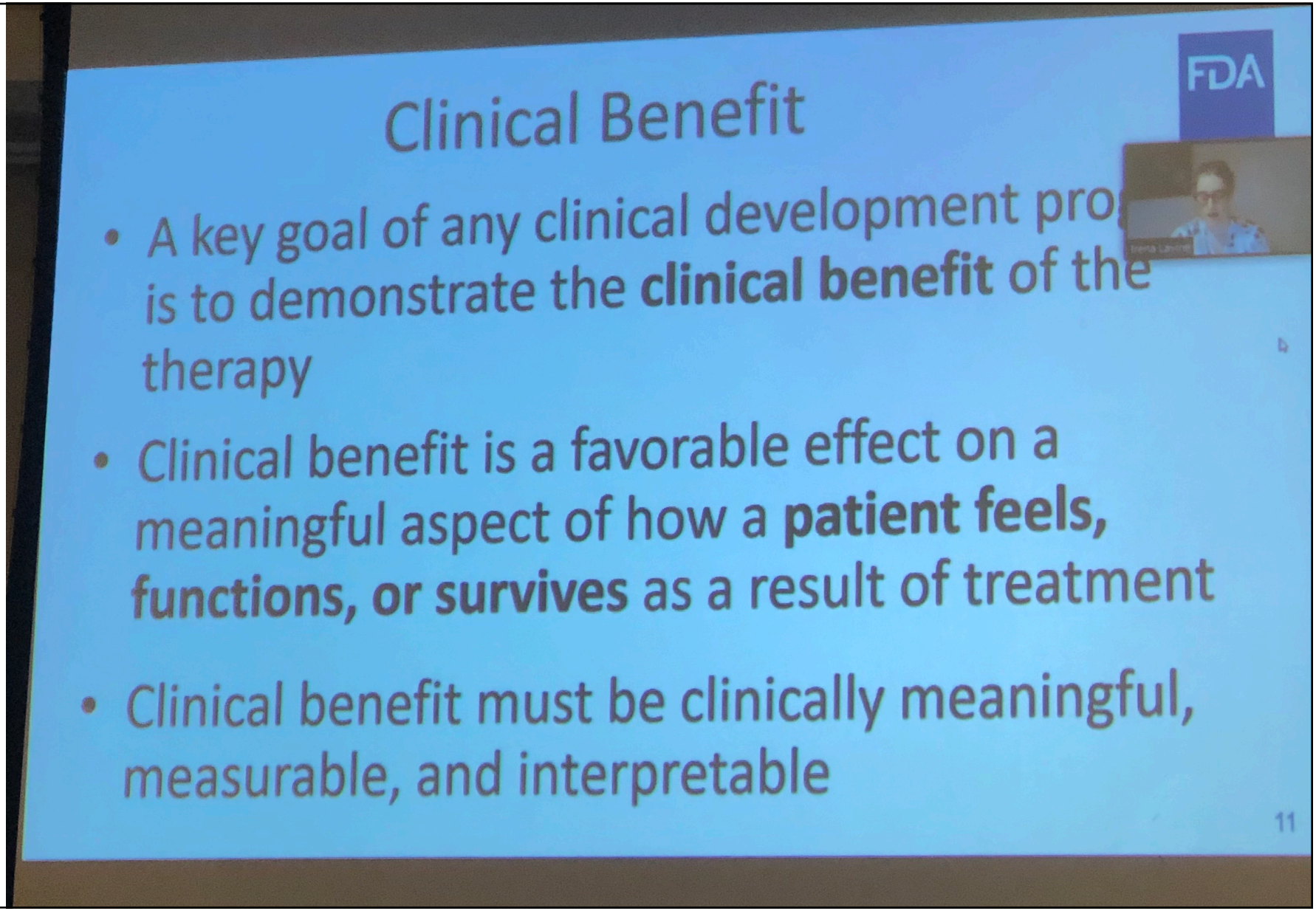
Inductive sites

Peyer's patch
(Mesenteric lymph node)

FDA

Irena Levine

March 7, 2020
Columbia Celiac Confernece



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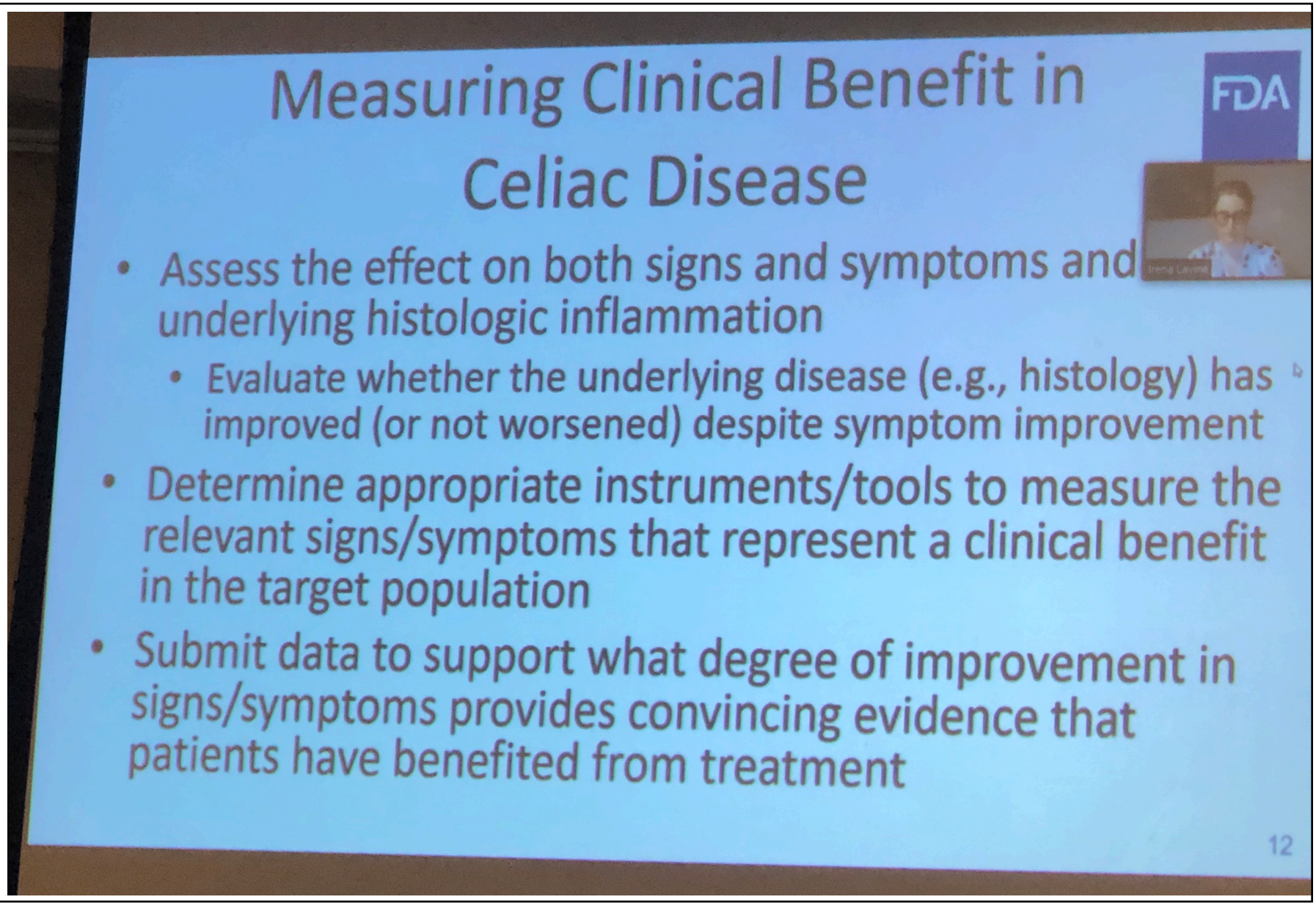

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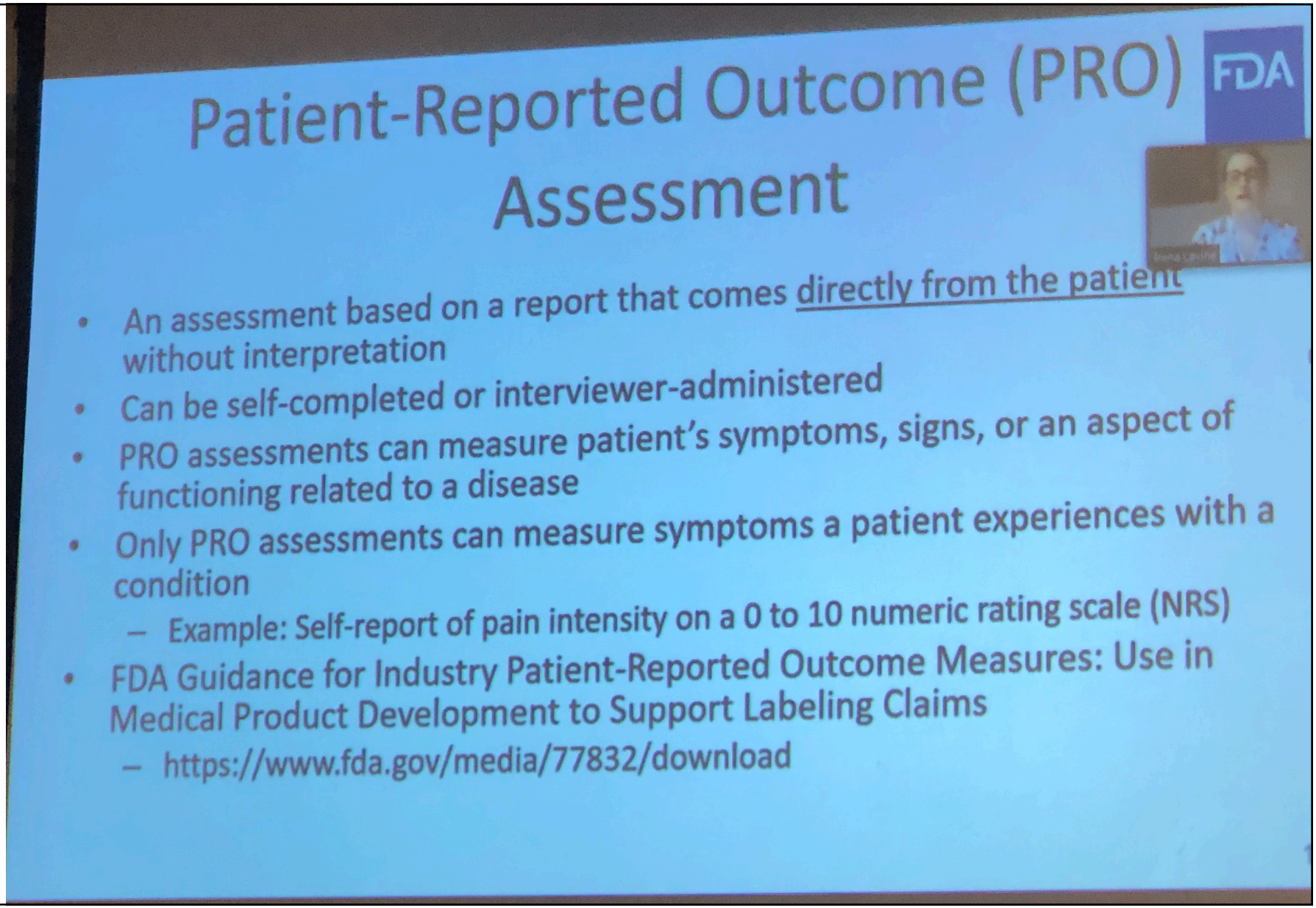

FDA ‘validated’ PROs (CeDPRO & CDSD)

	CeDPRO	CDSD
Abdominal cramping	X	
Abdominal pain	X	X
Bloating	X	
Constipation	X	X
Diarrhea	X	X
Flatulence	X	
Loose stool	X	
Nausea	X	X
Vomiting	X	
Headache	X	X
Tiredness	X	

Do not necessarily measure symptoms related to gluten induced immune activation in CeD patients

Symptoms
Masked (one off) food challenge w/vital gluten vs sham

TABLE 1 Symptoms on the day of sham and gluten challenges

	CeD PRO scores (0-10) Median (interquartile range)				Symptom occurrence Number (%) of patients out of 36 with item score ≥1			
	Sham	Gluten	Difference[a]	*P*-value[b]	Sham	Gluten	Difference[a]	*P*-value[c]
Nausea	0 (0-0)	5.5 (0-9)	4.5 (0-8)	<.001	4 (11)	25 (69)	21 (58)	<.001
Tiredness	1 (0-3)	4 (1-7)	1.5 (0-4)	.005	20 (56)	29 (81)	9 (25)	.063
Headache	0 (0-1)	2 (0-5)	1 (0-4)	.002	10 (28)	21 (58)	11 (31)	.075
Pain	0 (0-1)	1 (0-3)	0 (0-2)	.015	10 (28)	20 (56)	10 (28)	.055
Cramping	0 (0-1)	1 (0-4)	0 (0-2)	.017	9 (25)	19 (53)	10 (28)	.065
Diarrhoea	0 (0-0)	0 (0-5)	0 (0-2)	.021	7 (19)	17 (47)	10 (28)	.070
Loose Stool	0 (0-1)	0.5 (0-5)	0 (0-1)	.032	9 (25)	18 (50)	9 (25)	.065
Bloating	0 (0-2)	0.5 (0-3)	0 (0-2)	.292	15 (42)	18 (50)	3 (8)	.716
Gas	1 (0-1)	1 (0-3)	0 (−1 to 1)	.857	24 (67)	23 (64)	−1 (−3)	1

Daveson et al., APT 2020

Gluten challenge: Meaningful PROs

Short term (hours & days)

II ?

Long term (weeks and months)

Imminent question

In coeliac disease with detailed mechanistic insight (in contrast to many other immune mediated disease like T1D, IBD), should drug development be guided first and foremost by PROs?

What about biological surrogate markers?

Experimental non-dietary therapies for celiac disease (3/2020)

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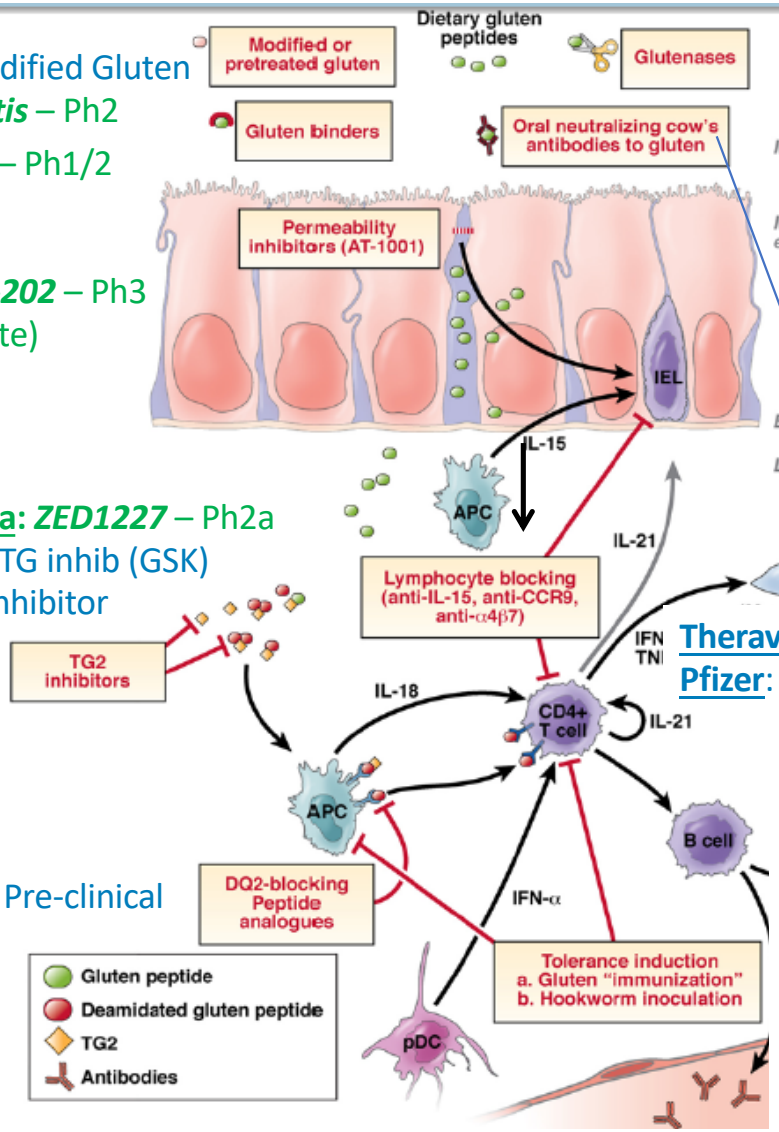

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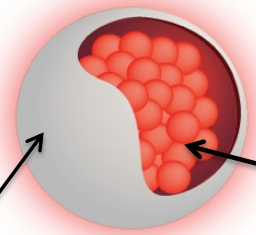
Fransisco Leon

GLUTEN TOLERANCE ACHIEVED WITH IMMUNE MODIFYING PARTICLES

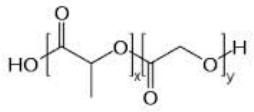
Tolerogenic Immune-Modifying Particles for Celiac (COUR-NP-GLI)

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



The Particle

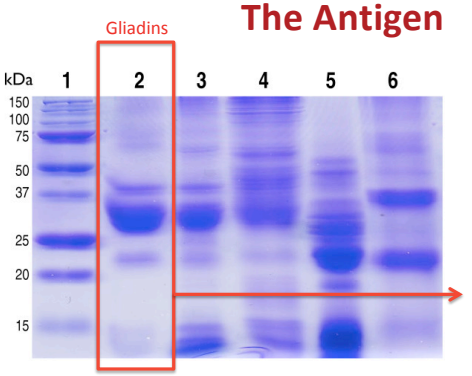
PLGA with proprietary surface modifications



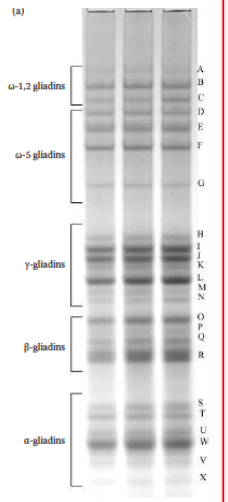
PLGA is biodegradable

Lactic Acid + Glycolic Acid

The Antigen



Identification of gliadin-binding peptides by phage display, Tingsu *et al*
Proteomic anlysis of wheat Gliadins Dziuba, *et al*

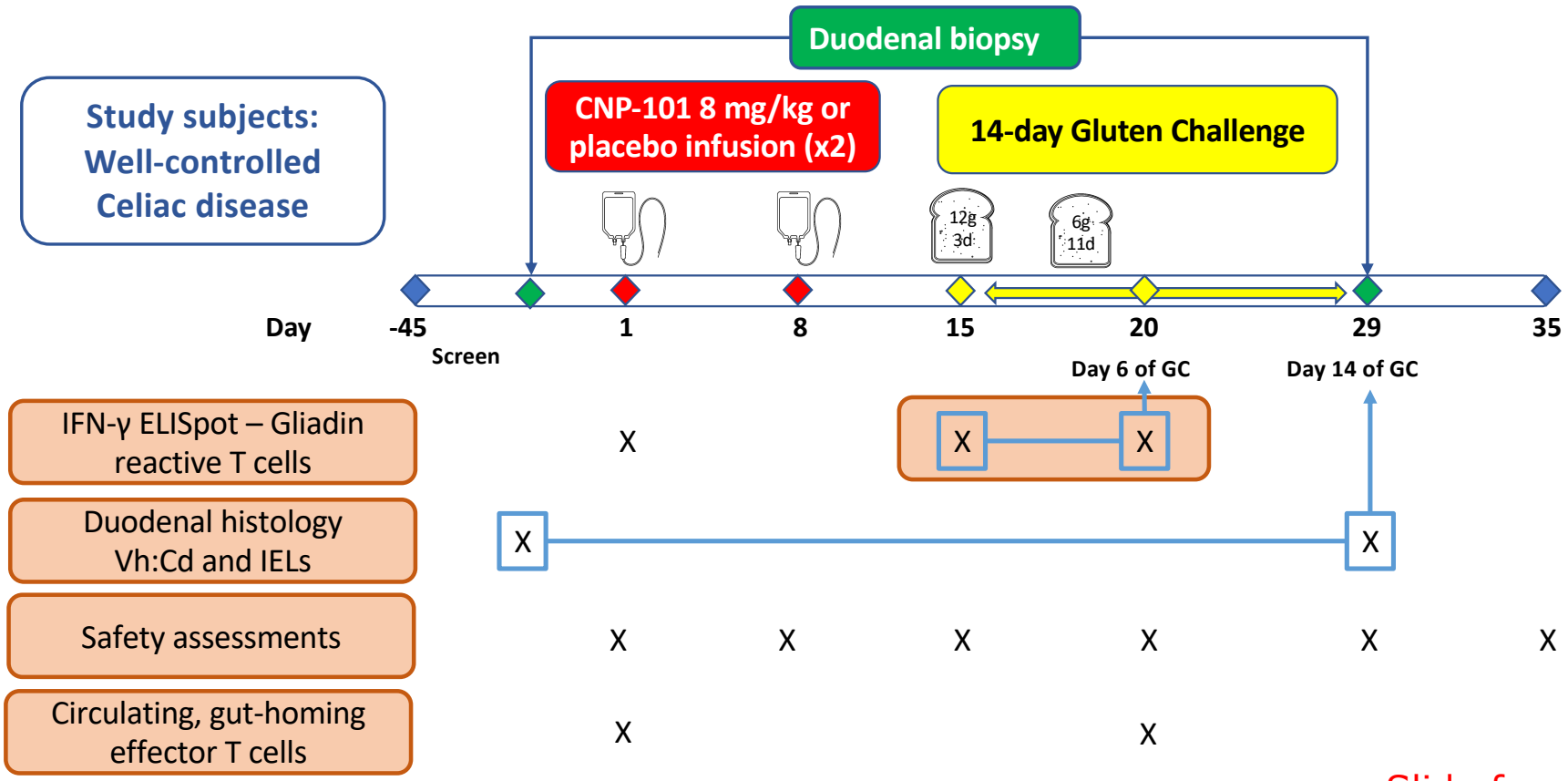


Particle (administered IV) is taken up via apoptotic pathway and trafficked to the spleen and processed by APCs.

Slide from C. Kelly

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

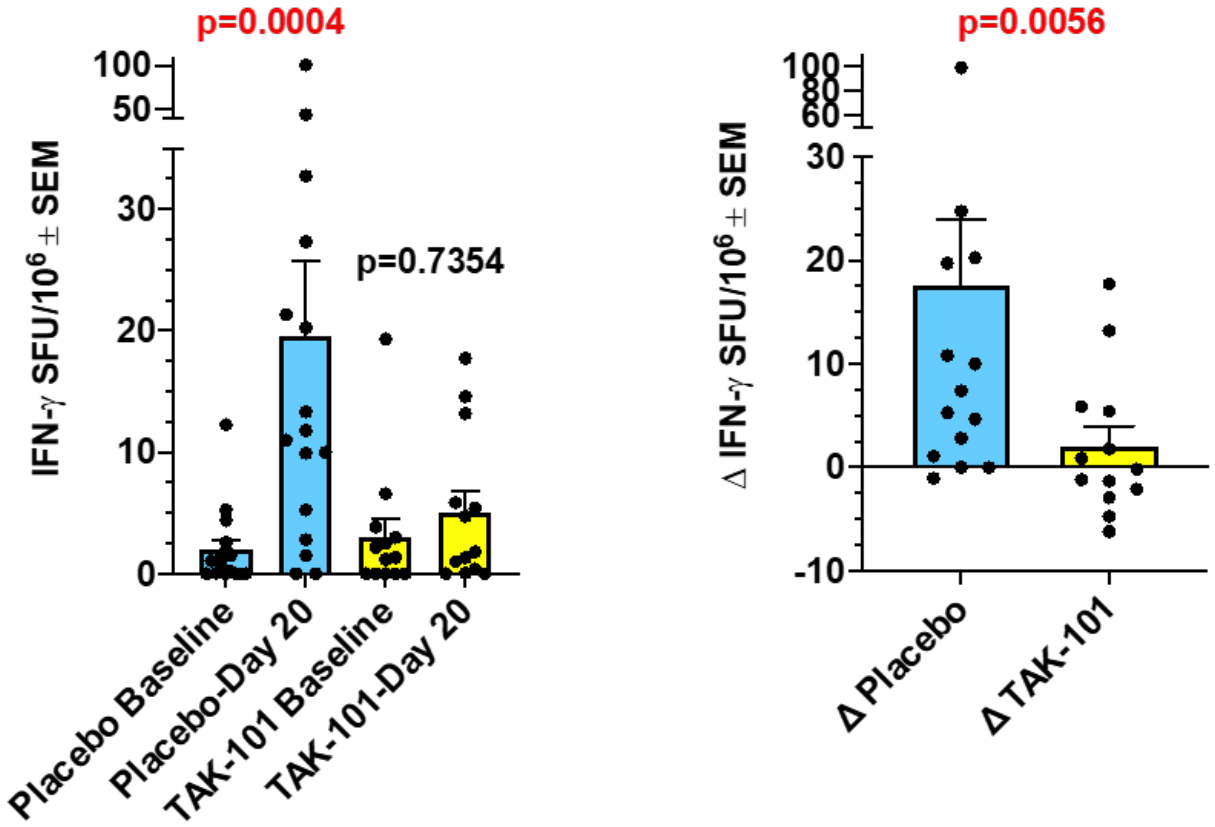
Phase 2a TAK-101 Proof-of-Concept study schematic



Slide from C. Kelly

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 met primary efficacy objective: reduced IFN-γ spot forming units response to gluten challenge

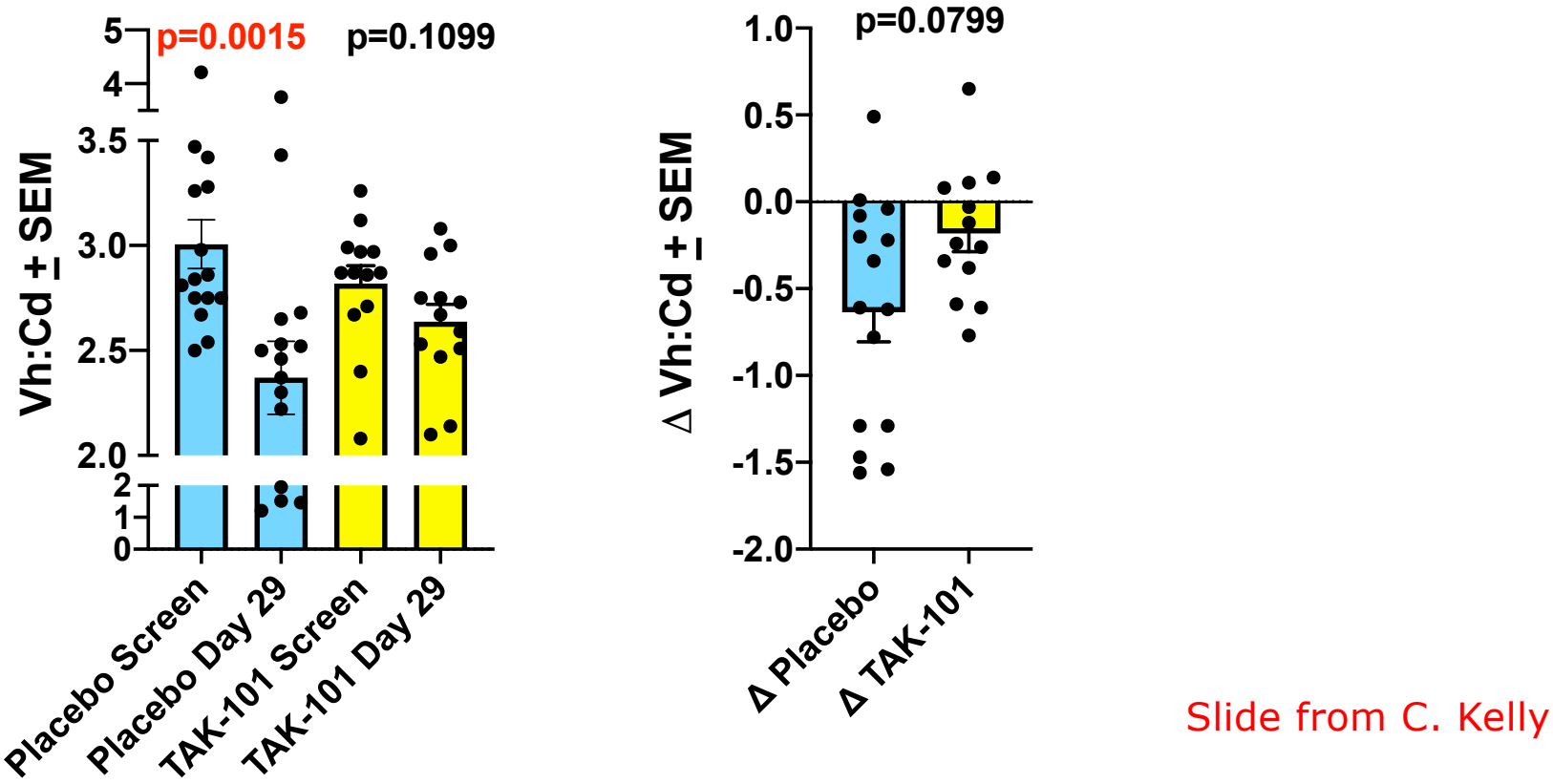


Slide from C. Kelly

Day 20 = 6 days after initiating Gluten Challenge

Baseline denotes Day 15 (or Day 1, if Day 15 sample inadequate)
ELISpot, enzyme-linked immunospot;
GC, gluten challenge; IFN, interferon; SFU, spot forming units

TMP-101 pre-treatment protects against histologic damage during gluten challenge



Slide from C. Kelly

GC, gluten challenge; Vh:Cd, villus height to crypt depth ratio

Day 29 = 15 days after initiating Gluten Challenge

CNP-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

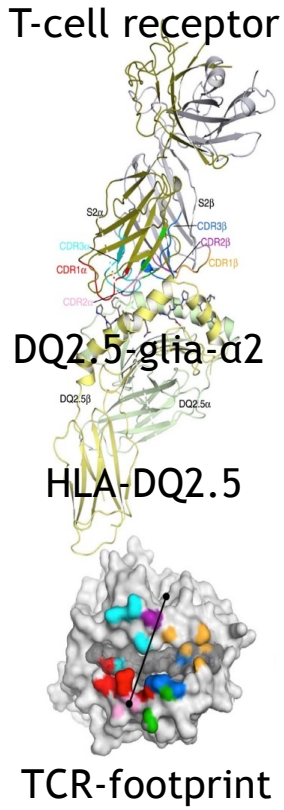
Phase 2a		
	CNP-101	Placebo
AE		
Nausea	81%	72%
Abdomen distention	56%	61%
Diarrhea	50%	50%
Headache	44%	17%
Abdominal pain	38%	28%
Vomiting	31%	33%
Fatigue	33%	50%
Back pain	31%	0%

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

Slide from C. Kelly

Nexvax2®
Short deamidated peptides for injection

Peptide	Length/Amino-acids	1st T cell epitope (seq)	2nd T cell epitope (seq)	Avidity for HLA-DQ2.5	Avidity for HLA-DQ8	Avidity for HLA-DQ2.2
NPL001	16	DQ2·5-glia-α1a PFPQPELPY	DQ2·5-glia-α2 PQPELPYPQ	Intermediate	Low	Negligible
NPL002	15	DQ2·5-glia-ω1 PFPQPEQPF	DQ2·5-glia-ω2 PQPEQPFPW	Intermediate	Negligible	Negligible
NPL003	16	DQ2·5-hor-3 PIPEQPQPY	*DQ2·5-glia-γ5* EQPIPEQPQ	Intermediate	Low	Negligible

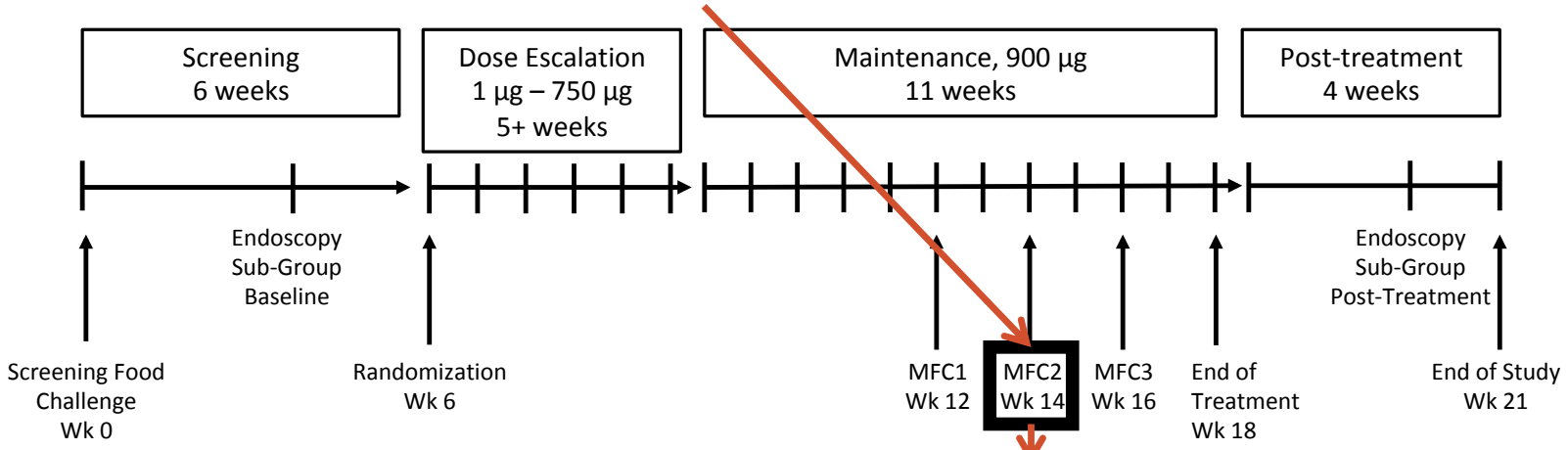


Slide from L. Williams/ R. Anderson

Goel G et al., *Lancet Gast Hepatol* 2017; Petersen J N et al., *Nat Struct Mol Biol* 2014

Study Design

Primary Objective: To evaluate the efficacy of Nexvax2 compared with placebo in reducing CeD-associated overall GI symptoms in CeD patients on GFD after the first masked food challenge containing gluten (6 grams).



Key eligibility criteria:
18 – 70 yo; HLA-DQ2.5; GFD > 1 year
Biopsy + serology diagnosis
GI symptoms after screening gluten challenge

Sites: USA (28), AUSTRALIA (9), NEW ZEALAND (4)

Primary endpoint, n=128
DQ2.5 non-homozygotes
1:1 Nexvax2:Placebo

Biopsy subgroup, n=50
DQ2.5 non-homozygotes
1:1 Nexvax2:Placebo

Exploratory, n=18
DQ2.5 homozygotes
2:1 Nexvax2:Placebo

Slide from
L. Williams/
R. Anderson

Primary endpoint not met

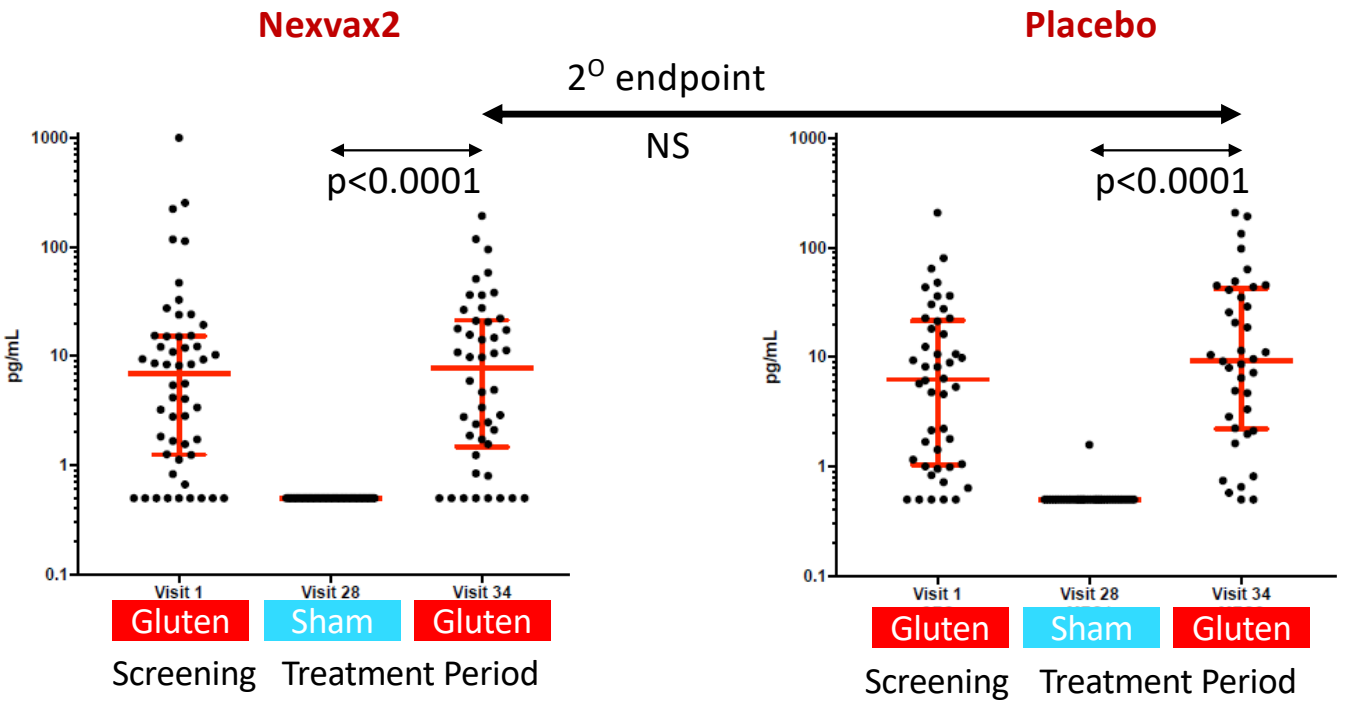
	Non-Homozygote (n=65)		Combined (n=88)	
Change from Baseline	**Total GI Score**	**Nausea**	**Total GI Score**	**Nausea**
Placebo: Mean (SEM)[a]	2.10 (0.44)	4.29 (0.71)	2.08 (0.40)	4.15 (0.66)
Nexvax2: Mean (SEM)[a]	2.74 (0.45)	4.81 (0.72)	2.51 (0.35)	4.38 (0.59)
Difference[a] **(90% CI)**	0.63 (-0.42, 1.68)	0.52 (-1.18, 2.21)	0.43 (-0.46, 1.31)	0.23 (-1.23, 1.70)
p-value (1-sided)[b]	0.8404	0.6933	0.7876	0.6040

a: Least-squares means from ANCOVA model with the baseline score as a covariate.

b: 1-sided p-value for change from baseline via an ANCOVA model with the baseline score as a covariate.

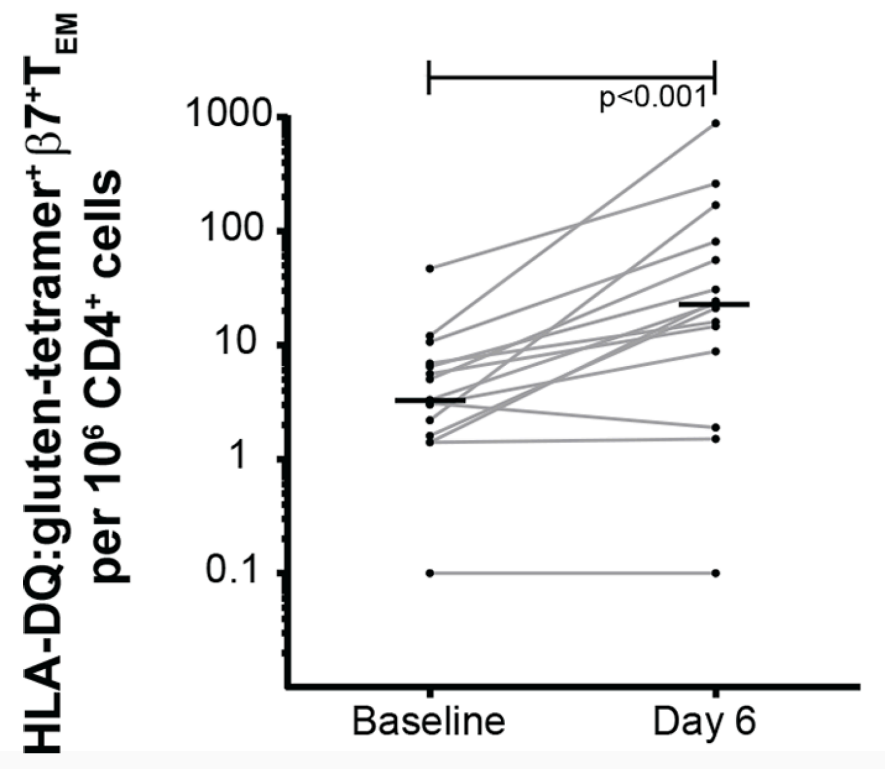
Slide from L. Williams/ R. Anderson

Secondary endpoint: Serum IL-2 4 h after gluten exposure

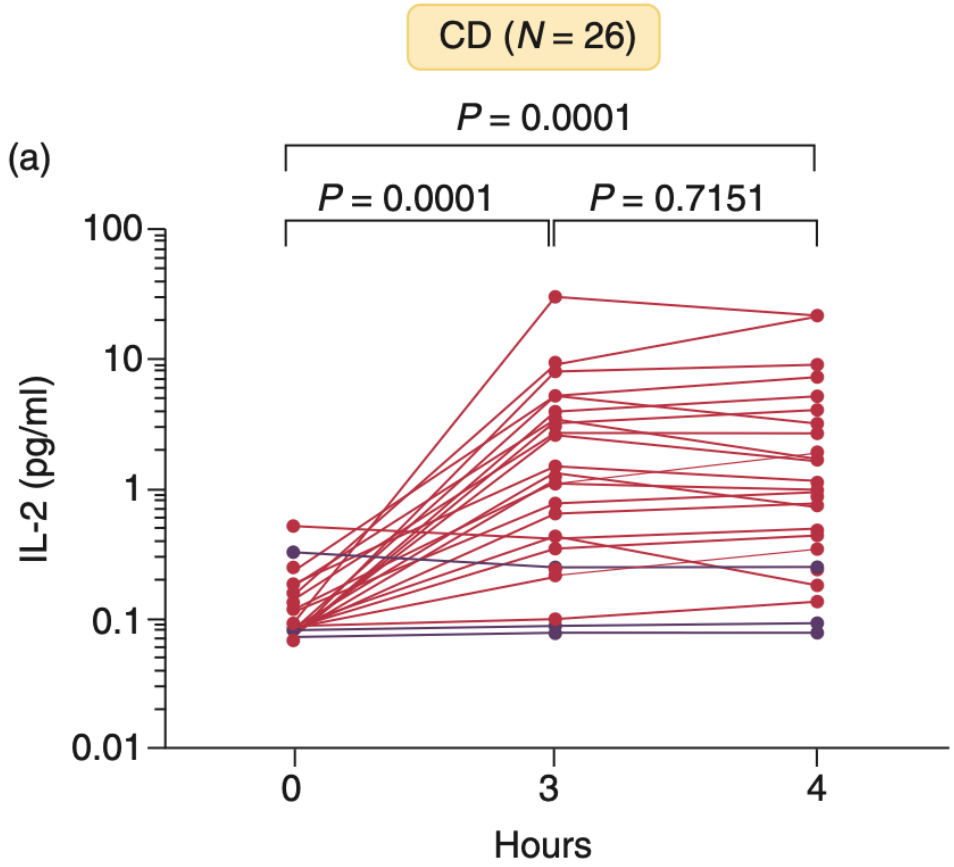


Slide from L. Williams/ R. Anderson

Gluten challenge: Large inter-individual variation in response for HLA-DQ:gluten tetramer and serum IL2

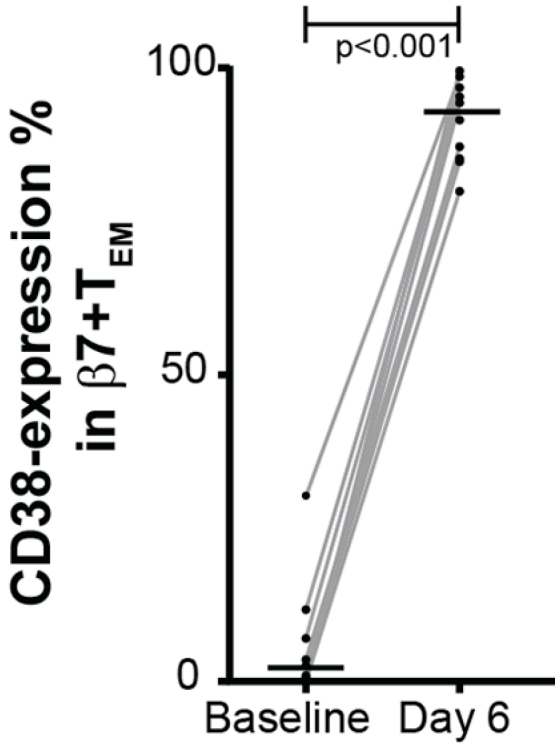


Sarna et al., Gut 2017



Tye-Din et al., UEG J 2020

Gluten challenge: Uniform increase in CD38 expression in blood on HLA-DQ:gluten tetramer cells



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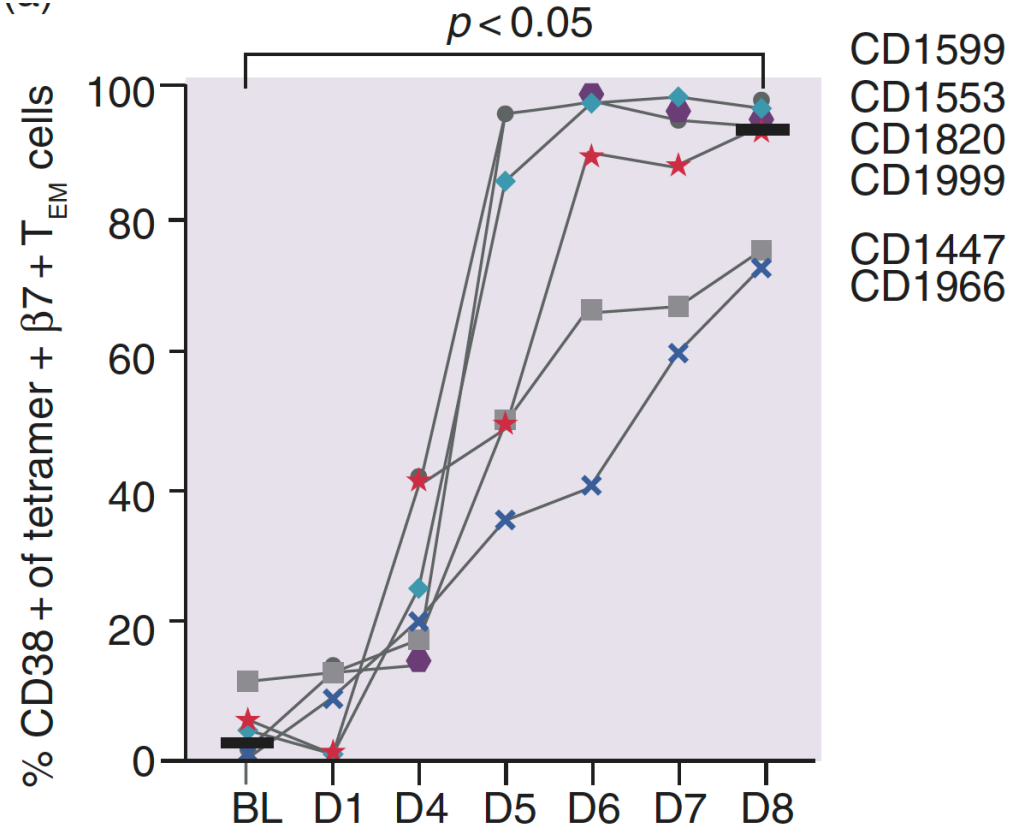

Zuehlke et al, UEG J 2019

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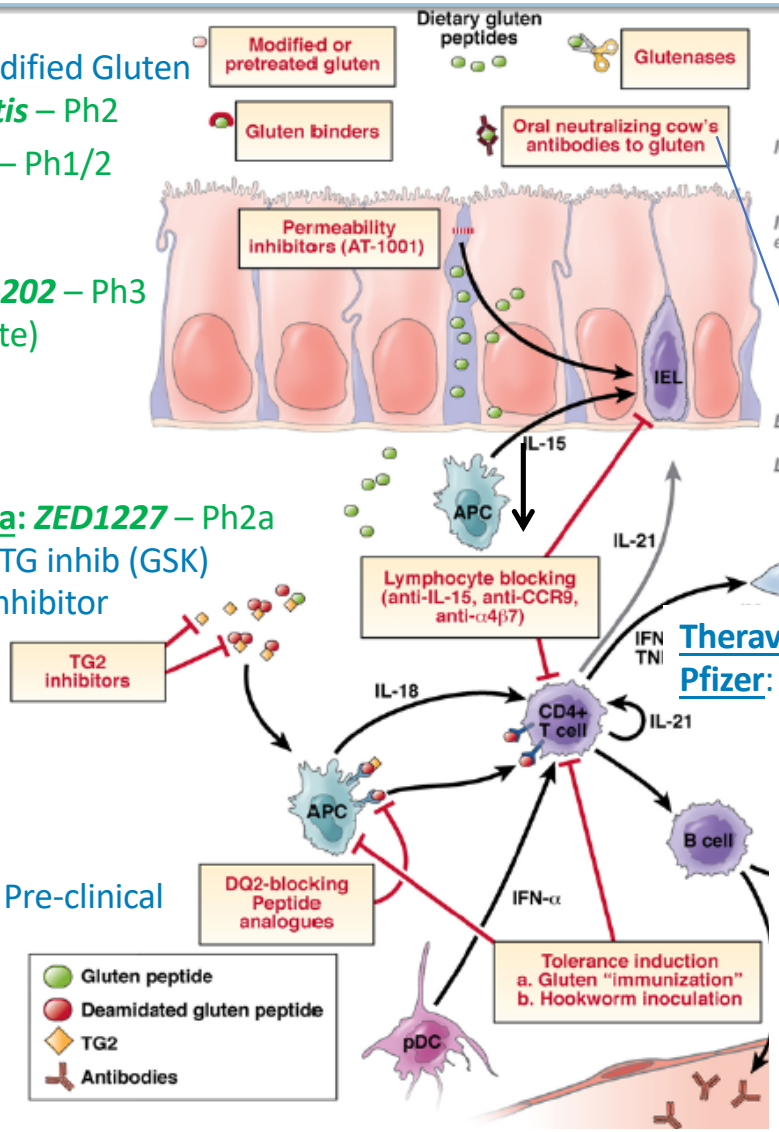

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