# Therapeutic advances in coeliac disease


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FOCiS Federation of Clinical Immunology Societies www.focisnet.org | CENTERS of EXCELLENCE

Coeliac UK Research Conference

London, March 9th 2016

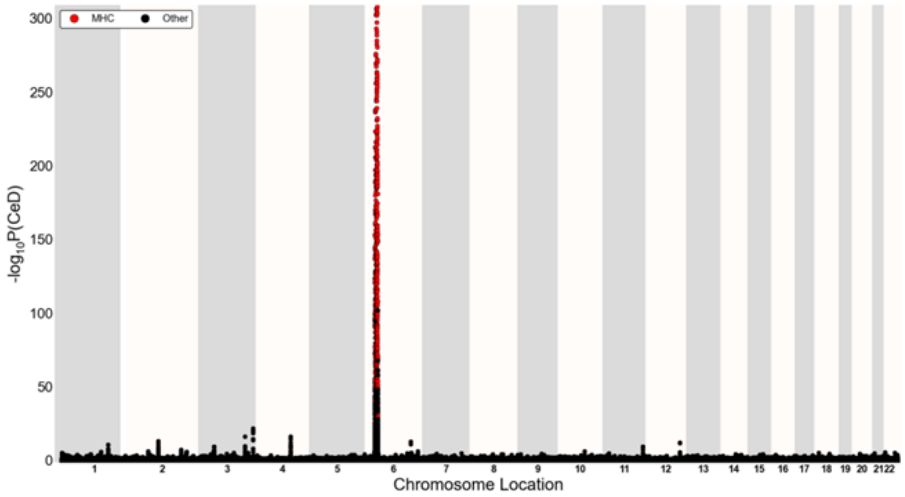
# CONFLICT OF INTEREST

Ludvig M. Sollid

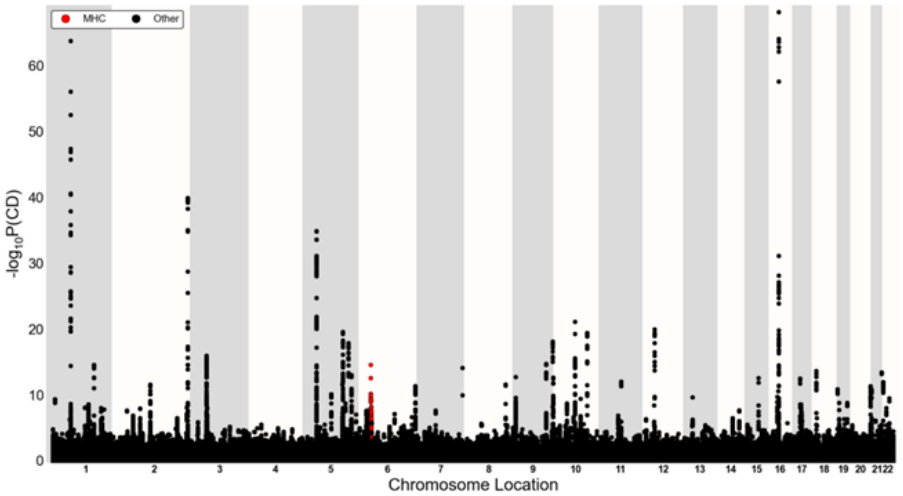
- Regeneron Pharma – Consulting / Funding
- ImmusanT Inc – Membership on adv. committee / Honoraria /Funding
- Alvine Pharma – Membership on adv. committee / Honoraria
- Glenmark Pharma – Consulting
- Celgene – Consulting

# GWAS and MHC (HLA)

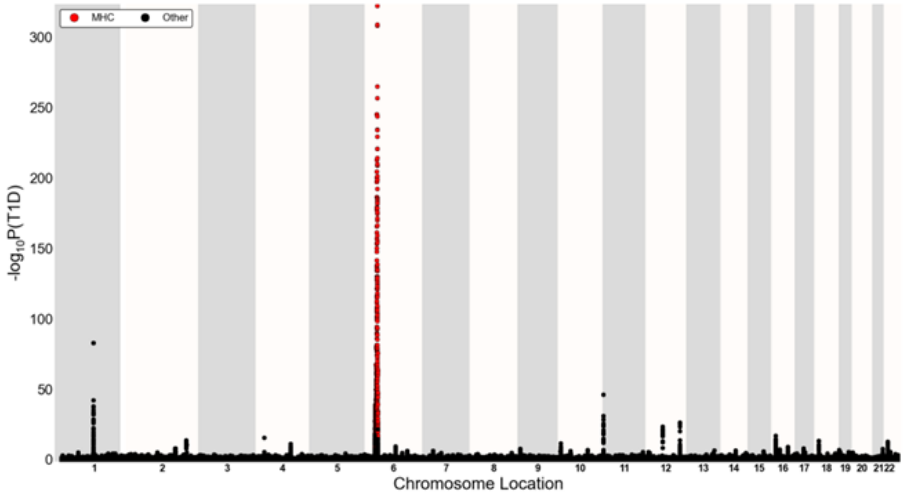
A. Celiac disease



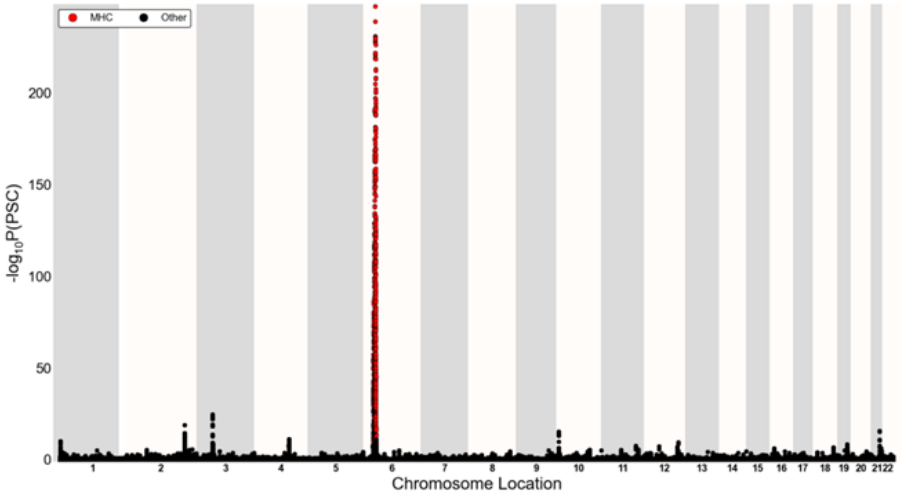

B. Crohn's disease




C. Type 1 diabetes

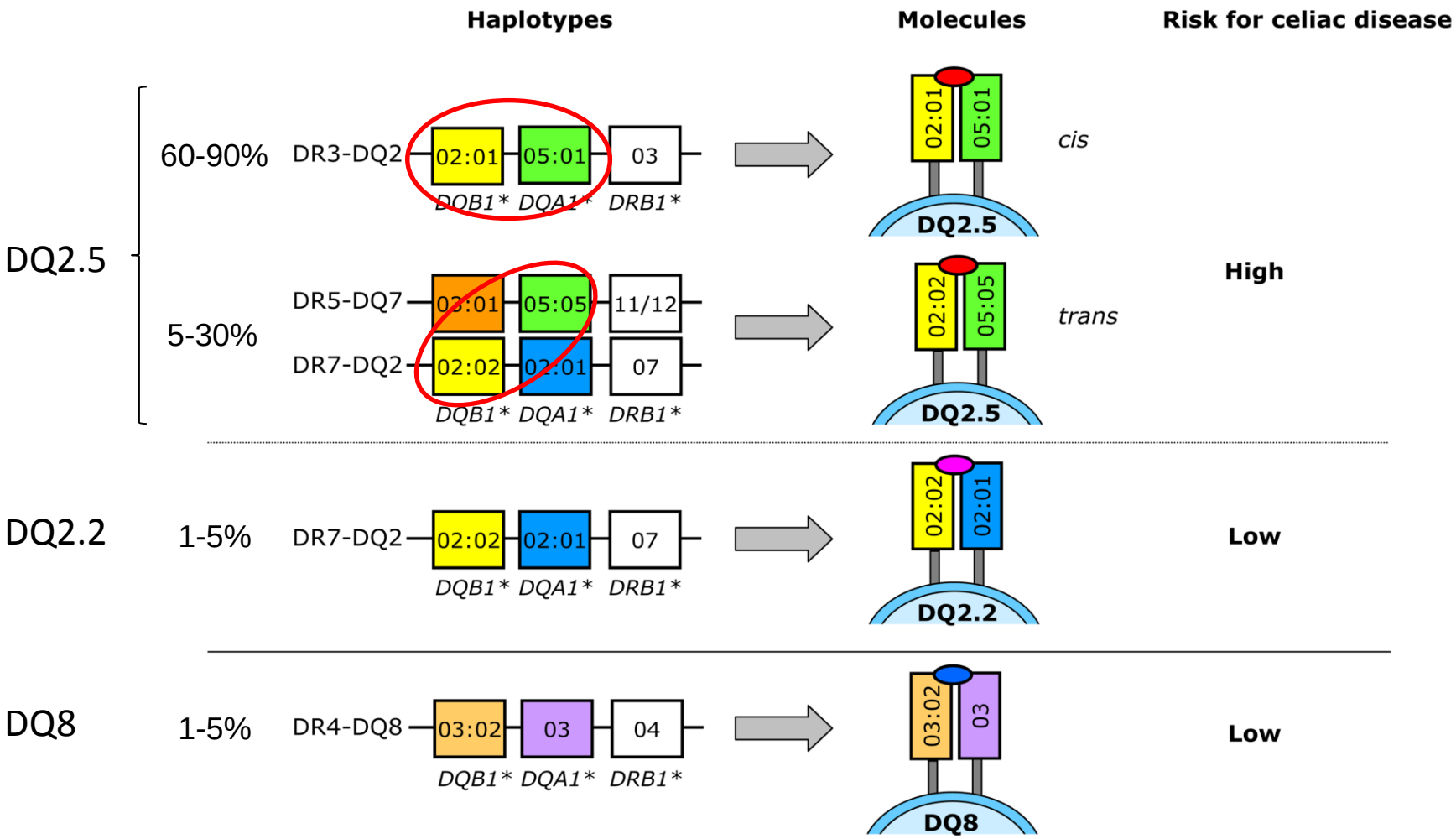



D. Primary sclerosing cholangitis

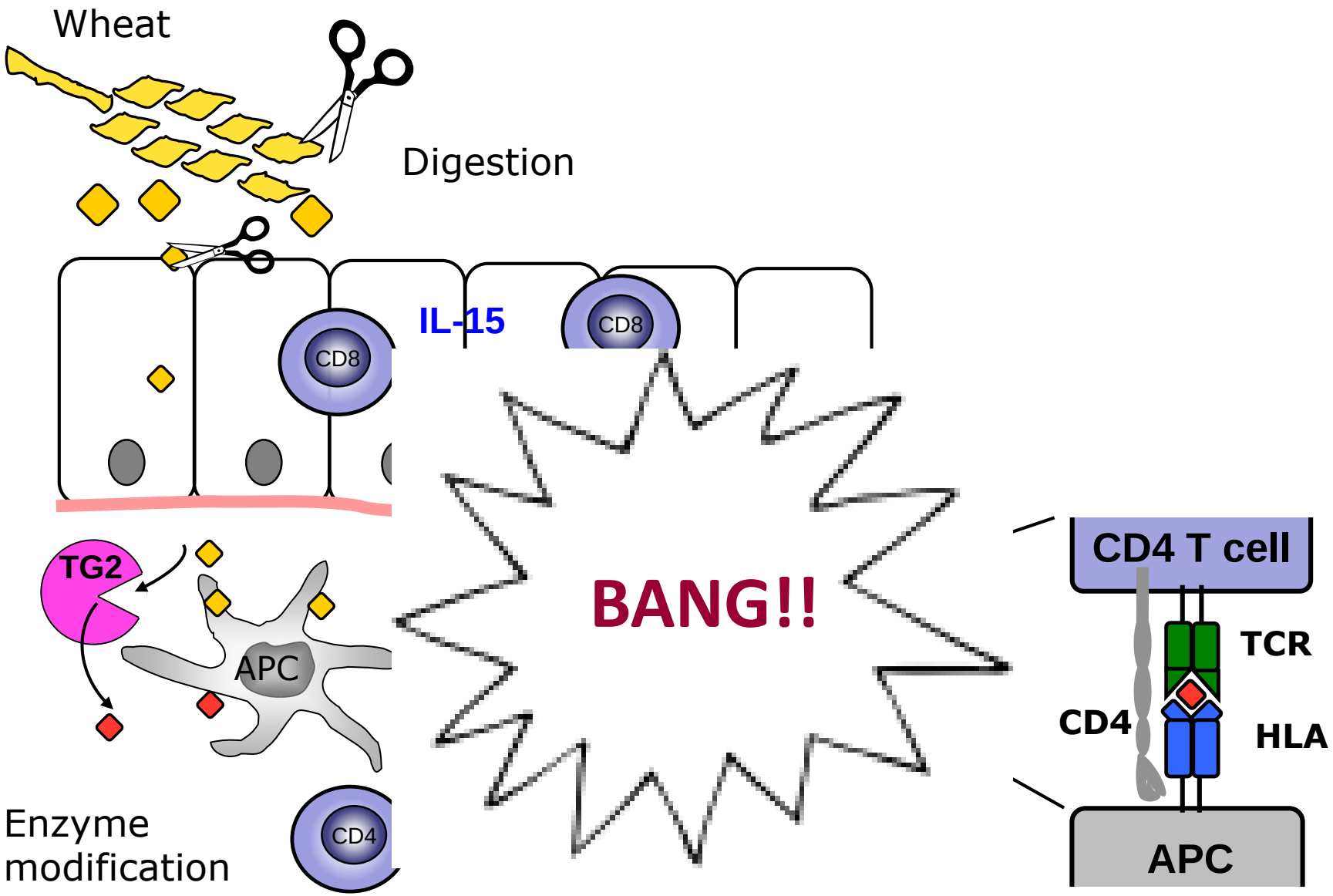



Slide courtesy: TH Karlsen

# HLA association in coeliac disease



# The coeliac lesion

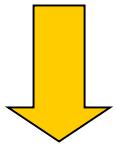


# Generation of T-cell epitopes in the gut

α2-gliadin (AJ133612)

```
  1 MVRVPVPQLQ PQNPSQQQPQ EQVPLVQQQQ FPGQQQPFPP QQPYPQPQPF PSQQPYLQLQ
 61 PFPQPQLPYP QPQLPYPQPQ LPYPQPQPFR PQQPYPQSQP QYSQPQQPIS QQQQQQQQQQ
121 QQKQQQQQQQ QILQQILQQQ LIPCRDVVLQ QHSIAYGSSQ VLQQSTYQLV QQLCCQQLWQ
181 IPEQSRCQAI HNVVHAIILH QQQQQQQQQQ QQPLSQVSFQ QPQQQYPSGQ GSFQPSQQNP
241 QAQGSVQPQQ LPQFEEIRNL ALETLPAMCN VYIPPYCTIA PVGIFGTNYR
```

Transglutaminase (QXP)



digestive enzymes

```
61 PFPQPQLPYP QPQLPYPQPQ LPYPQPQP                    LQLQ
```

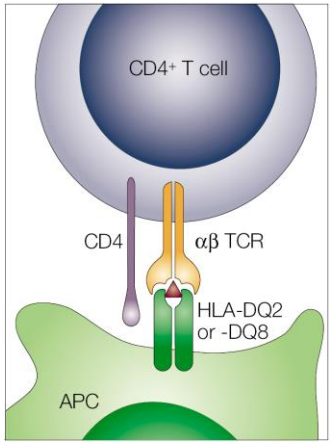
after transglutaminase treatment

```
61 PFPQPELPYP QPELPYPQPE LPYPQPQPF                  LQLQ
```

peptide (33 amino acids)

```
PFPQPELPY
  PQPELPYP Q
       PYP QPELPY
         P QPELPYPQ
              PYPQPE LPY
                PQPE LPYPQ
```

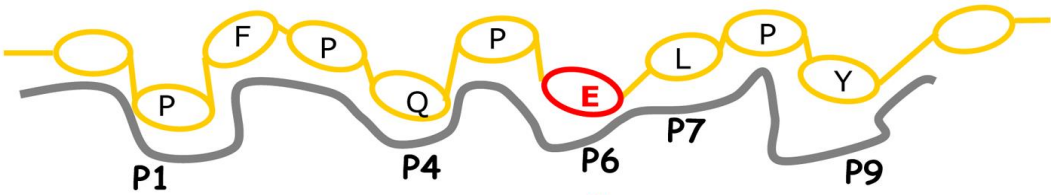
6 copies of
T cell epitopes




Shan et al, Science 2002; Arentz-Hansen et al, Gastroenterology 2002

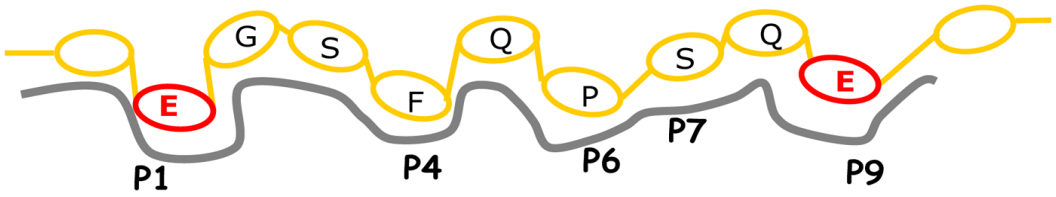
# HLA-DQ2.5 and HLA-DQ8 restricted gluten T-cell epitopes

## DQ2.5



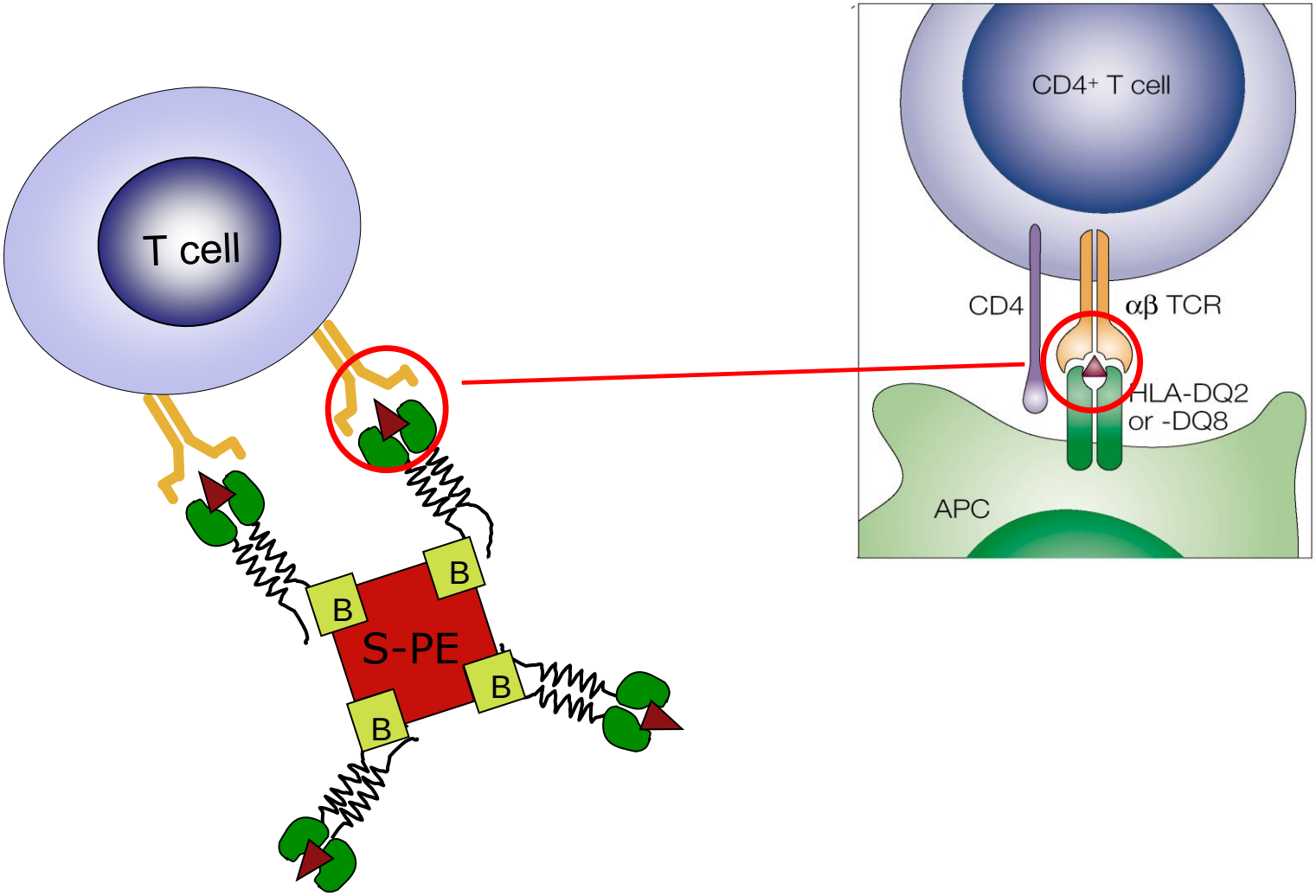

| | P1 | | P4 | | P6 | P7 | | P9 |
|---|---|---|---|---|---|---|---|---|
| DQ2.5-glia-α1b | P | Y | P | Q | P | **E** | L | P | Y |
| DQ2.5-glia-α2 | P | Q | P | **E** | L | P | Y | P | Q |
| DQ2.5-glia-α3 | F | R | P | **E** | Q | P | Y | P | Q |
| DQ2.5-glia-γ1 | P | Q | Q | S | F | P | **E** | Q | Q |
| DQ2.5-glia-γ2 | I | Q | P | **E** | Q | P | A | Q | L |
| DQ2.5-glia-γ3 | Q | Q | P | **E** | Q | P | Y | P | Q |
| DQ2.5-glia-γ4a | S | Q | P | **E** | Q | **E** | F | P | Q |
| DQ2.5-glia-γ4b | P | Q | P | **E** | Q | **E** | F | P | Q |
| DQ2.5-glia-γ4c | Q | Q | P | **E** | Q | P | F | P | Q |
| DQ2.5-glia-γ4d | P | Q | P | **E** | Q | P | F | C | Q |
| DQ2.5-glia-γ5 | Q | Q | P | F | P | **E** | Q | P | Q |
| DQ2.5-glia-ω1 | P | F | P | Q | P | **E** | Q | P | F |
| DQ2.5-glia-ω2 | P | Q | P | **E** | Q | P | F | P | W |
| DQ2.5-glut-L1 | P | F | S | **E** | Q | **E** | Q | P | V |
| DQ2.5-glut-L2 | F | S | Q | Q | Q | **E** | S | P | F |
| DQ2.5-hor-1 | P | F | P | Q | P | **E** | Q | P | F |
| DQ2.5-hor-2 | P | Q | P | **E** | Q | P | F | P | Q |
| DQ2.5-hor-3 | P | I | P | **E** | Q | P | Q | P | Y |
| DQ2.5-sec-1 | P | F | P | Q | P | **E** | Q | P | F |
| DQ2.5-sec-2 | P | Q | P | **E** | Q | P | F | P | Q |
| DQ2.5-ave-1a | P | Y | P | E | Q | **E** | E | P | F |
| DQ2.5-ave-1b | P | Y | P | E | Q | **E** | Q | P | F |

## DQ8

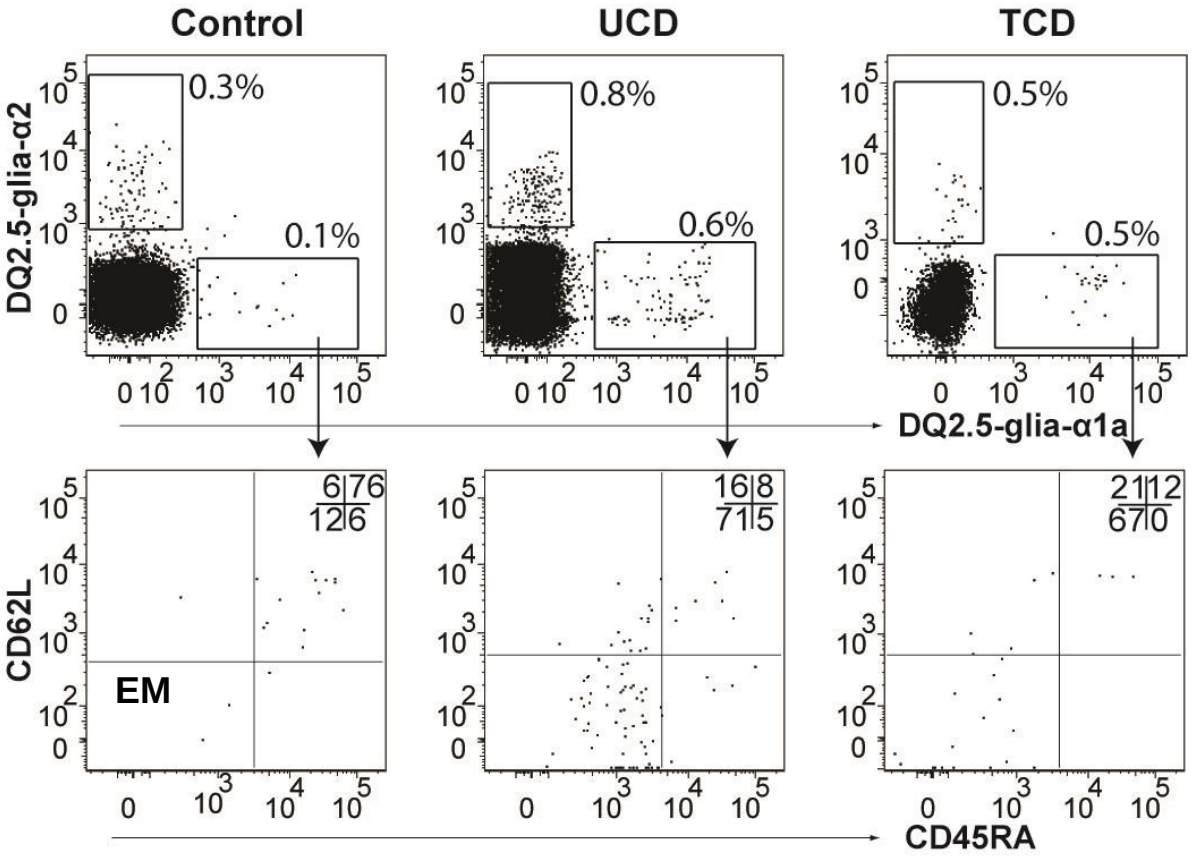


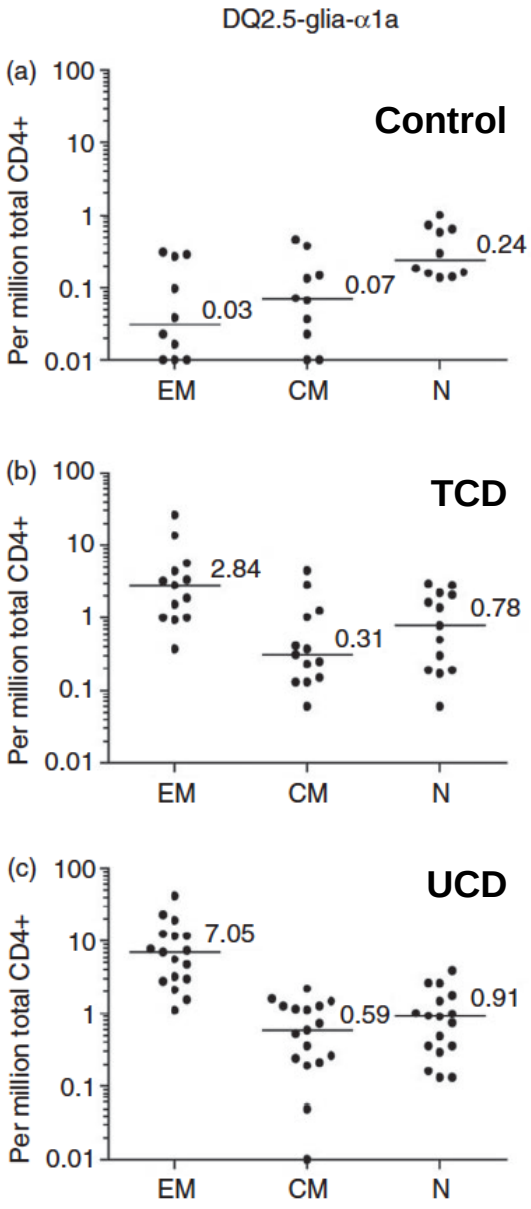

| | P1 | | P4 | | P6 | P7 | | P9 |
|---|---|---|---|---|---|---|---|---|
| DQ8-glia-γ1a | **E** | Q | P | Q | Q | P | F | P | Q |
| DQ8-glia-γ1b | **E** | Q | P | Q | Q | P | Y | P | **E** |
| DQ8-glut-H1 | Q | G | Y | Y | P | T | S | P | Q |

# HLA-DQ2.5-gluten epitope tetramers



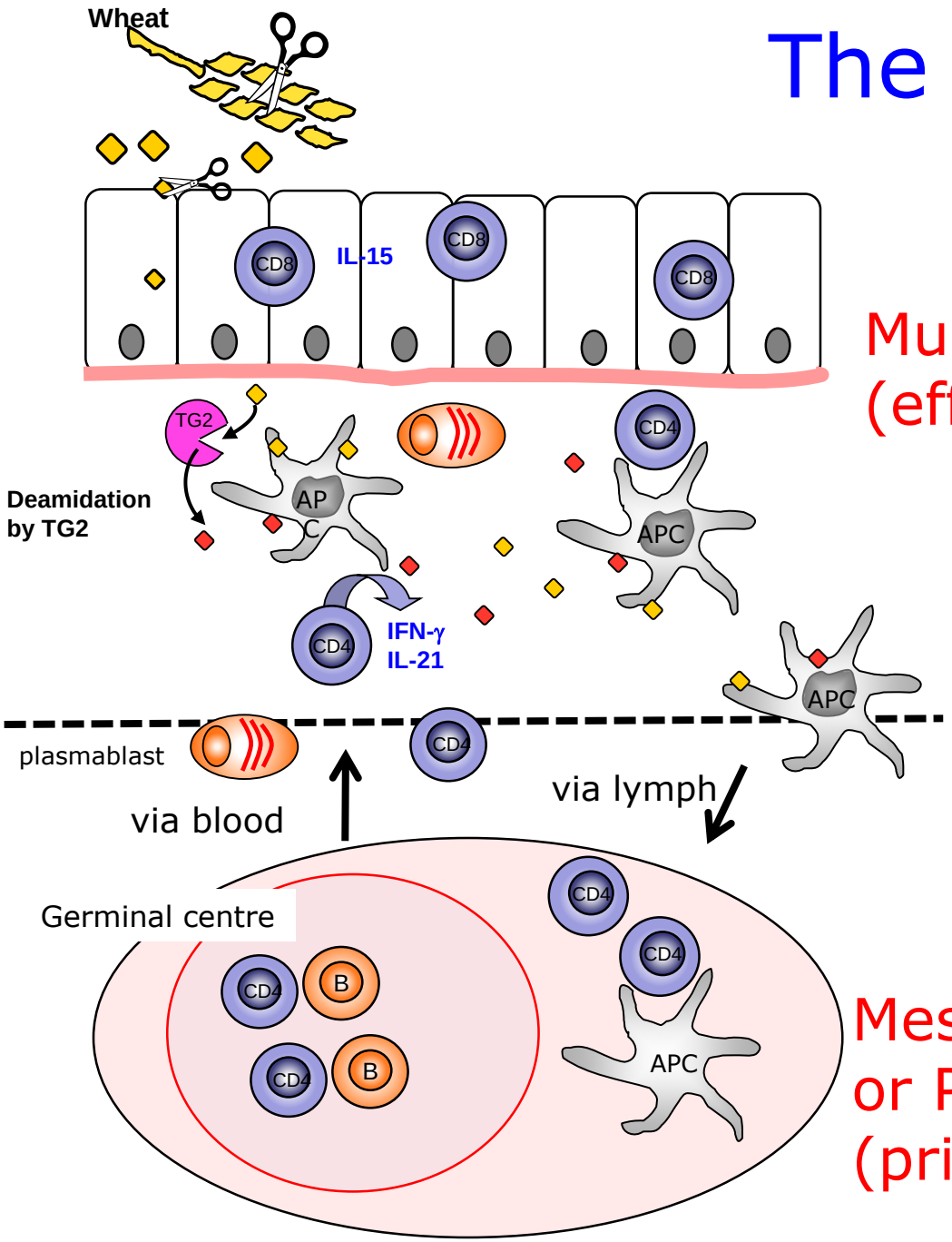
# Increased frequency of gluten-specific effector-memory CD4+ T cells in coeliac disease



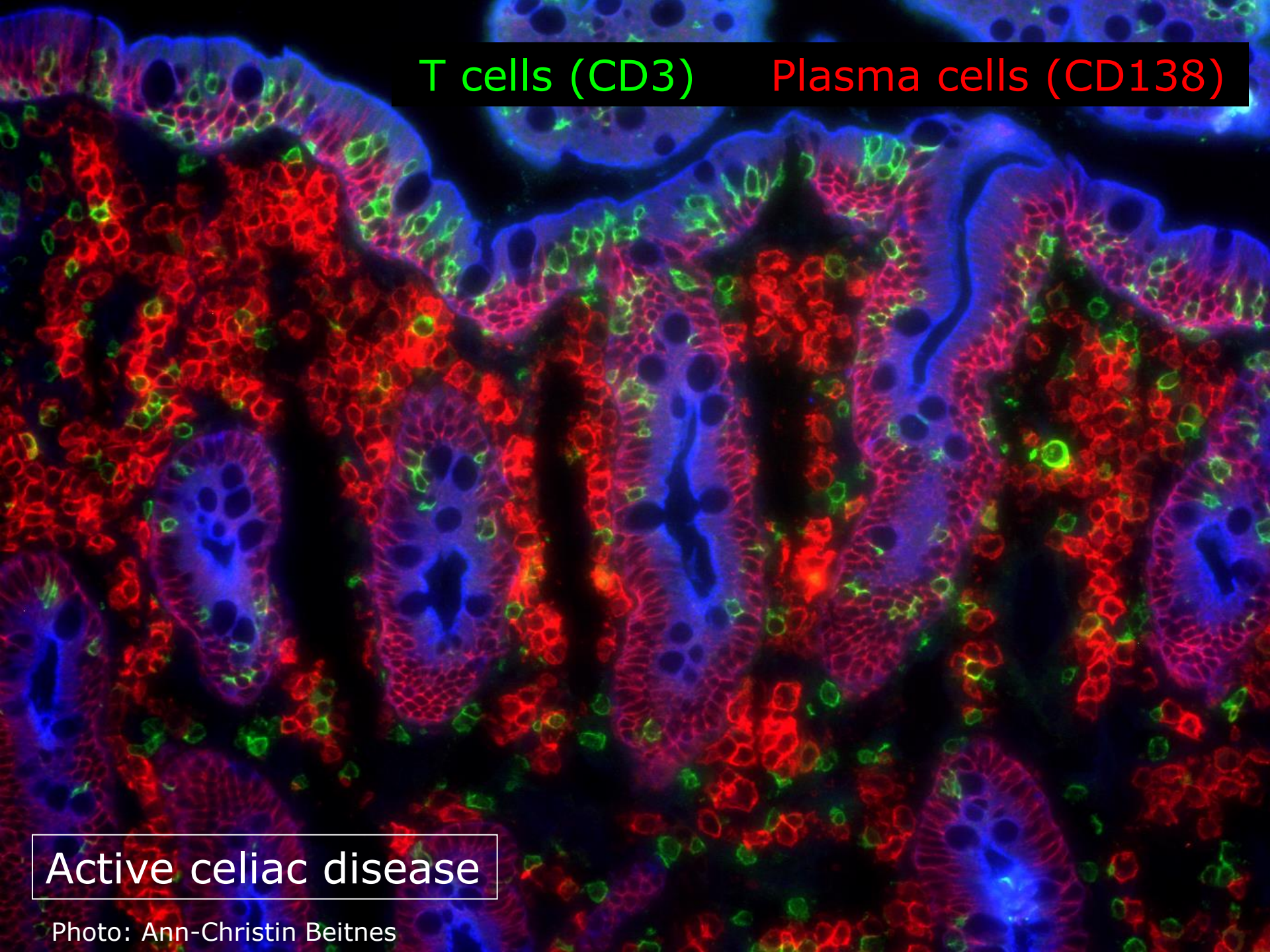

Christophersen et al., UEG J 2014

# The celiac lesion

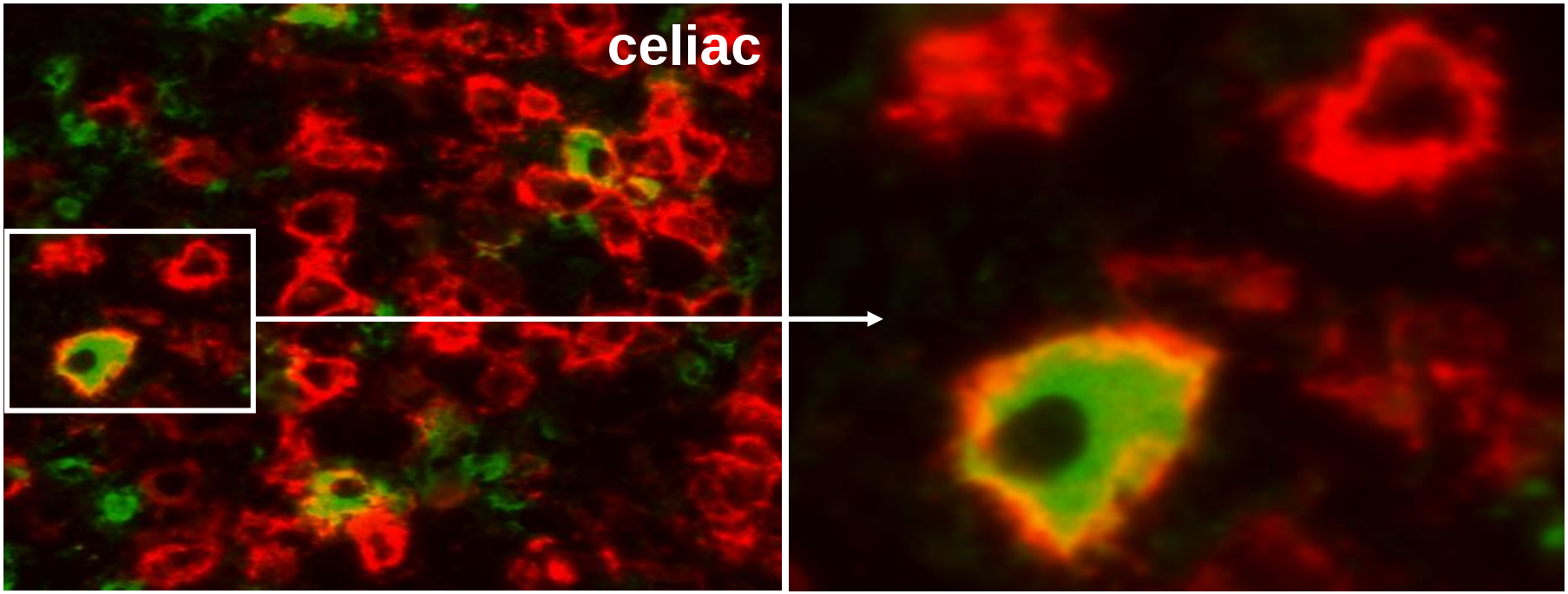



Mucosa
(effector site)

Mesenteric lymph node
or Peyer's patch
(priming site)

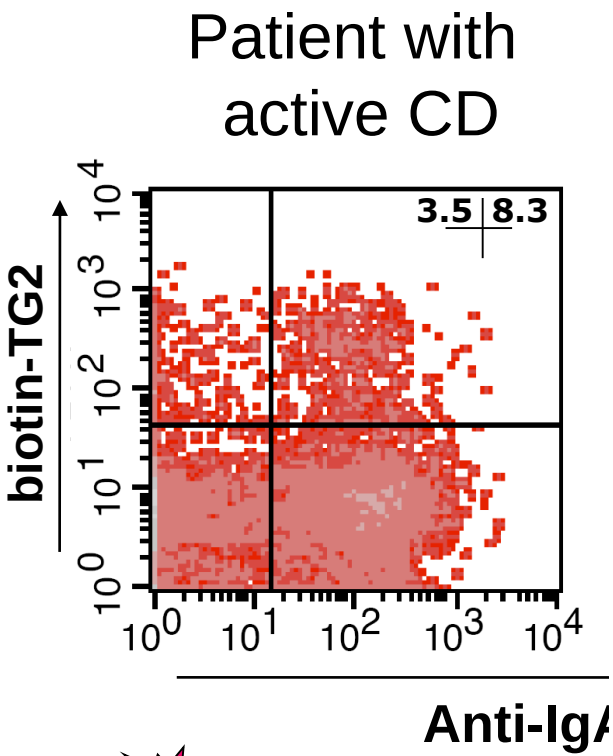

T cells (CD3)
Plasma cells (CD138)
Active celiac disease
Photo: Ann-Christin Beitnes

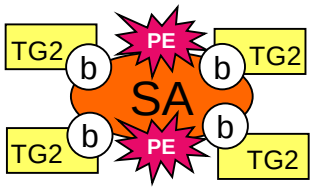
# Visualization of TG2-specific plasma cells by immunofluorescence on intestinal cryosections

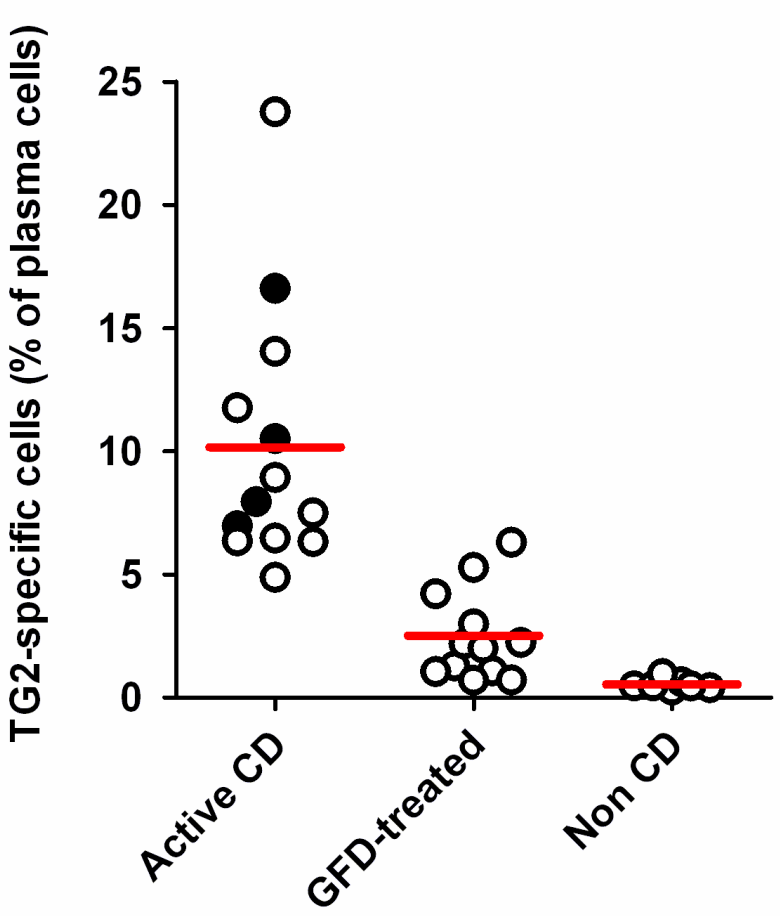



Di Niro et al., Nat Med 2012

# Detection of TG2-specific plasma cells by flow cytometry on intestinal cell suspensions




Di Niro et al., Nat Med 2012

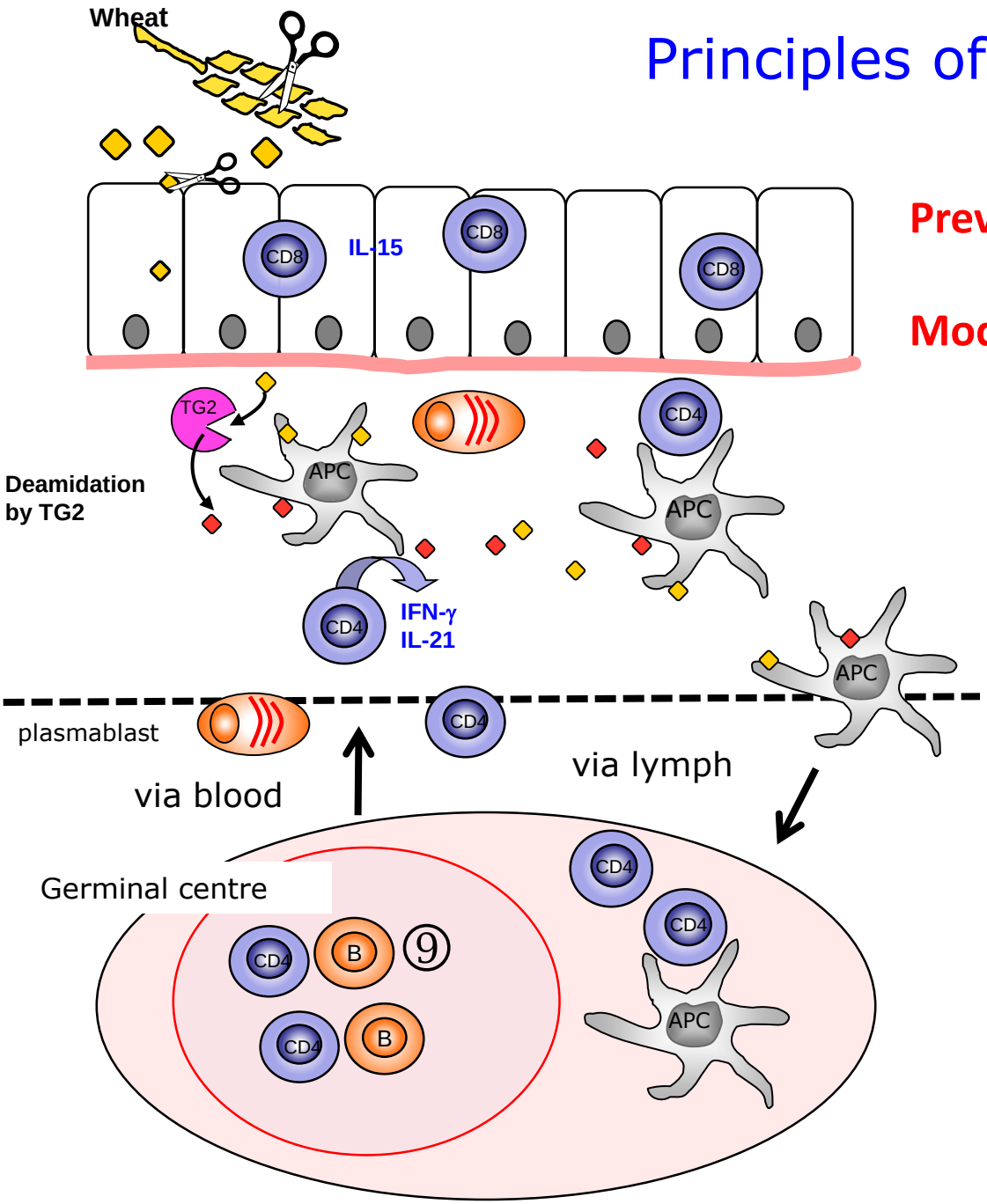
# Key event in the pathogenesis of coeliac disease

Clonal expansion of:

- Gluten specific CD4+ T cells
- TG2 specific B cells
- Gluten specific B cells

The point of T- and B-cell clonal expansions is when the patient is crossing the bridge.

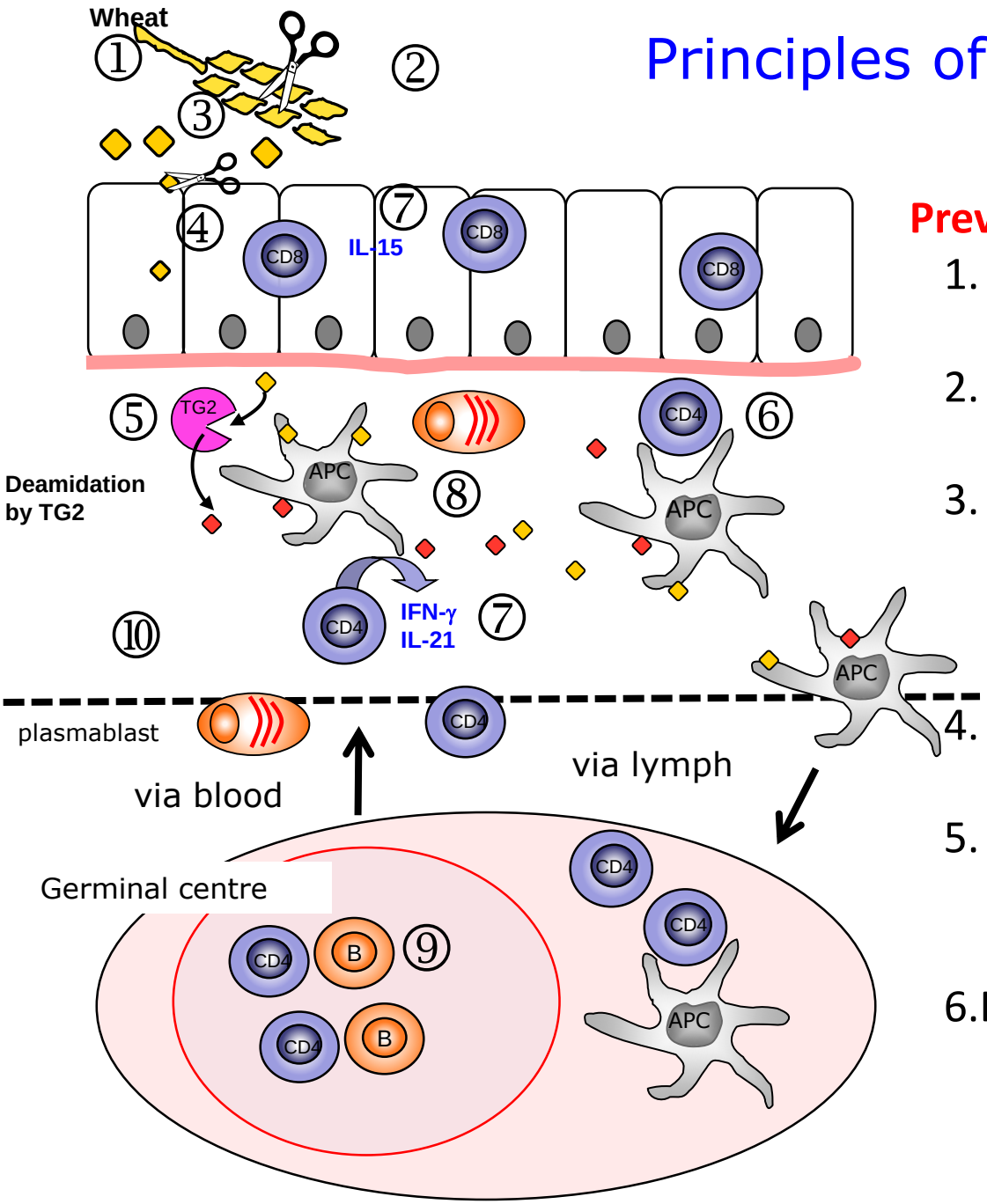
# Principles of therapies for CD




**Prevent gluten from stimulating T cells**

**Modify immune response**

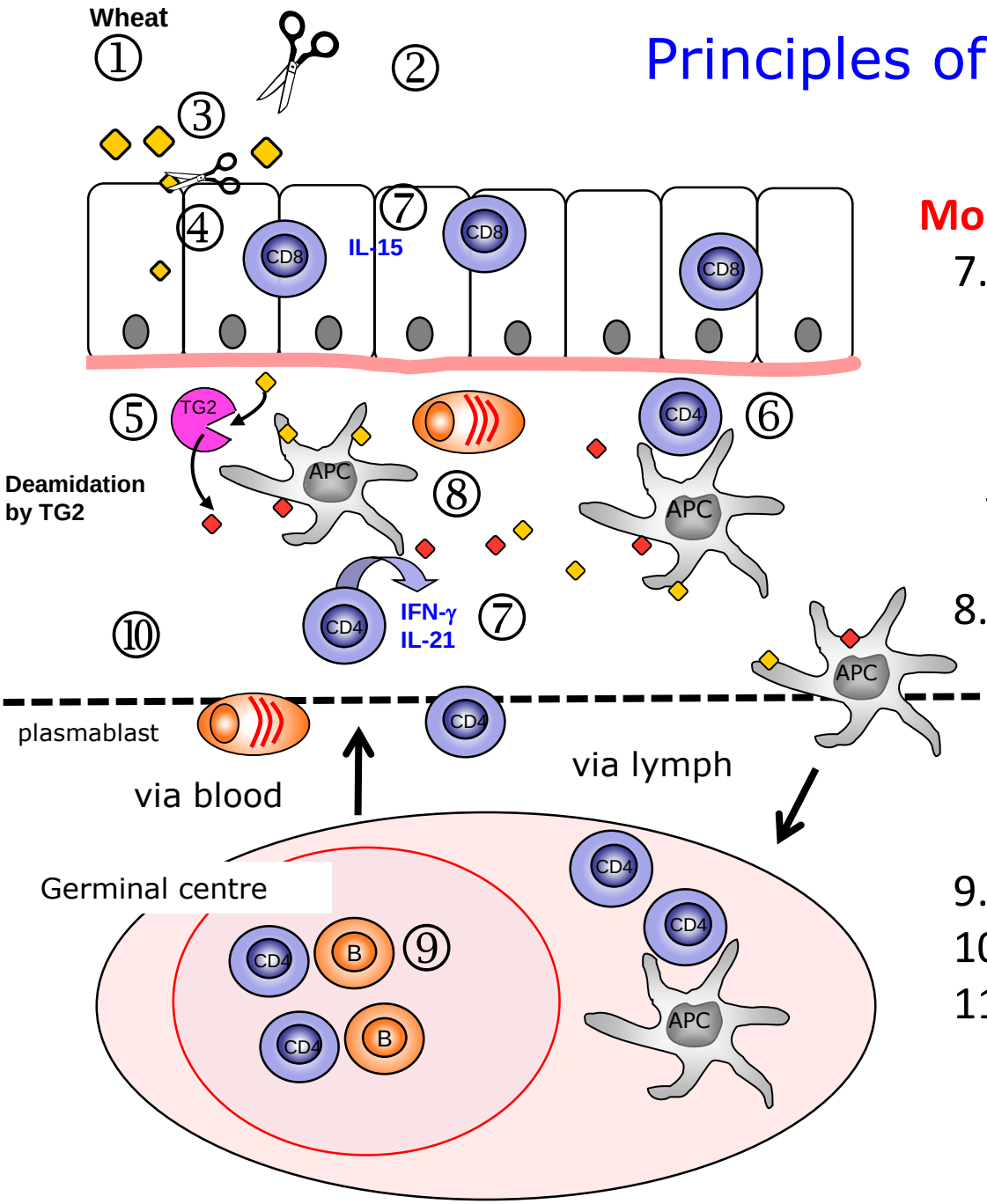
# Principles of therapies for CD




**Prevent gluten from stimulating T cells**

1. Grain/gluten modification
   - Microbial transglutaminase
2. Polymers sequestering gluten
   - BL-7010: BioLine Rx
3. Glutenases
   - Alv003: Alvine
   - AN-PEP: DSM
   - Kuma030
4. Epithelial barrier
   - INN-202: AlbaTherapeutics
5. Transglutaminase inhibitors
   - Dr. Falk
   - Sitari Inc
6. Blocking HLA-peptide presentation
   - RG7625 (Cat S inhib): Roche

# Principles of therapies for CD




**Modify immune response**

7. Anti-cytokine therapy
   - Anti-IL15:
     - AMG 714: Celimmune
     - CALY-002: Calypso
   - Anti-IL2/IL15RB
     - Hu-Mik-b 1: NCI
8. Immune modulation therapy
   - Nexvax2 (peptides): ImmusanT
   - RBC med. tolerisation: Kayano
   - Nanoparticles: Cour Pharma
   - Hookworm
9. Anti-B cell therapy (anti-CD20)
10. Blocking intestinal homing
11. Topical steroids

ALVINE
PHARMACEUTICALS, INC.

# CeliAction Study®
# Top-Line Results

A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Dose-Ranging Study of the Efficacy and Safety of ALV003 Treatment in Symptomatic Celiac Disease Patients Maintained on a Gluten-Free Diet

# CeliAction Study® Design

- Study Population
  - N ~ 500; Bx-proven celiac disease; GFD ≥ 1 year
  - Self reported history of moderate or severe symptoms associated with gluten exposure
- Study Design
  - Randomized, placebo controlled, dose ranging
  - Stratified by serostatus to assure balance randomization of TG2-IgA+ patients
  - 4-week run-in
  - Baseline, 12-week treatment, Post-Rx duodenal Bx
- Endpoints
  - Primary: ∆ Vh:Cd; Secondary: Symptoms (PRO), IEL, QOL, Serologies

# Overall Summary of Results

- Efficacy:
  - ALV003 appeared to have little effect on the primary or secondary endpoints
    - Patients in all treatment groups showed improved adherence to their gluten-free diets
- Safety:
  - No obvious study treatment-related adverse event trends observed
- Patient Reported Outcomes:
  - CDSD© measures were sensitive to change in symptom frequency and severity (e.g., abdominal pain, bloating, nausea, diarrhea, tiredness)
  - Symptom improvement (compared to placebo) appeared more commonly in seropositive patients treated with higher doses at weeks 6 and 12 with directional trends in seronegative and overall populations
- Likely Explanation:
  - Trial effect obscured any potential treatment effect by reduction of ALV003 substrate in the diet
    - Altered patient behavior a result of administering drug TID, filling out CDSD© daily, which appears to have resulted in improved compliance with GFD
- Manuscript detailing the results – in preparation (DC Adelman et al)

# Drug development – clinical trials

Phase 0: Pharmacodynamics and pharmacokinetics in humans
Phase 1: Screening for safety
Phase 2: Establishing efficacy of drug, usually against placebo
Phase 3: Final confirmation of safety and efficacy
(Phase 4: Sentry studies during sales)

From: en.wikipedia.org

Standard approval process: 7-10 years

FDA: Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review

**Fast track:** Process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need.

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Example: "Heart attack" AND '

Search for studies:

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March 4, 2016

**69 studies found for:** celiac disease | Interventional Studies | Phase 1, 2, 3, 4, 0

**Modify this search** | How to Use Search Results

INN-202 (Alba Therapeutics): Begins phase 3 (Fast Track) trials in late 2016