



# Postbiotici e celiachia: Dalla disbiosi alla modulazione metabolica della mucosa intestinale

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> [Science](#). 1999 Mar 5;283(5407):1535-8. doi: 10.1126/science.283.5407.1535.

FULL TEXT LINKS

Science  
AAAAA

ACTIONS

## Adhesive and mammalian transglutaminase substrate properties of *Candida albicans* Hwp1

> [Lancet](#). 2003 Jun 21;361(9375):2152-4. doi: 10.1016/s0140-6736(03)13695-1.

## Is *Candida albicans* a trigger in the onset of coeliac disease?

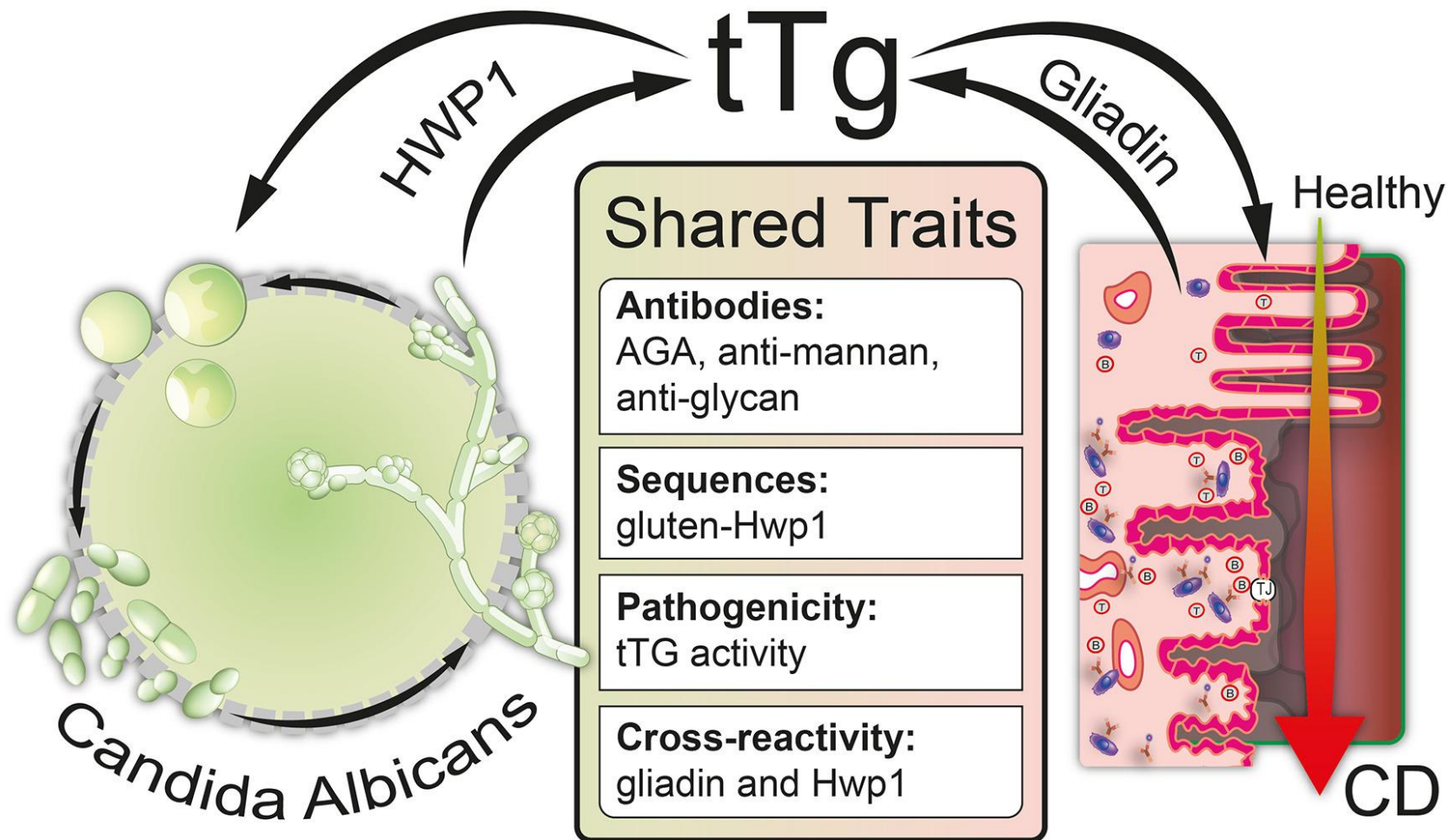
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## *Candida albicans* in celiac disease: A wolf in sheep's clothing

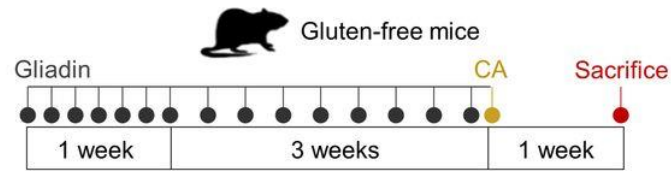
Lerner Aaron  , Matthias Torsten [Show more](#) ✓

## *Candida* e celiachia: la narrazione

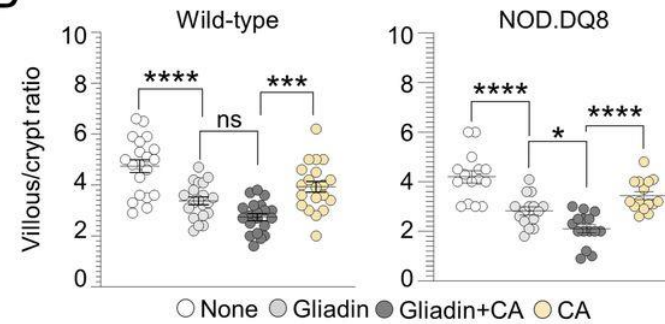
- The hyphal wall protein 1 (HWP) is a transglutaminase substrate, and is used by *C. albicans* to adhere to the intestinal epithelium
- HWP1 contains aminoacid sequences that are identical or highly homologous to known coeliac disease-related alpha-gliadin and gamma-gliadin T-cell epitopes.
- Tissue transglutaminase and endomysium components could become covalently linked to the yeast.
- *C. albicans* might function as an adjuvant that stimulates antibody formation against HWP1 and gluten, and formation of autoreactive antibodies against tissue transglutaminase and endomysium.



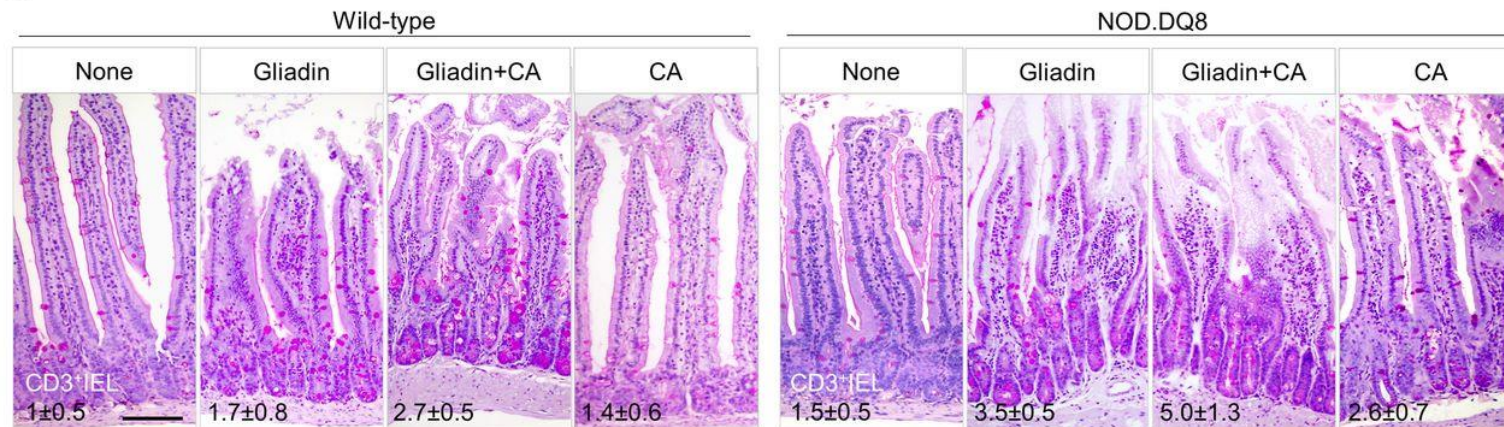
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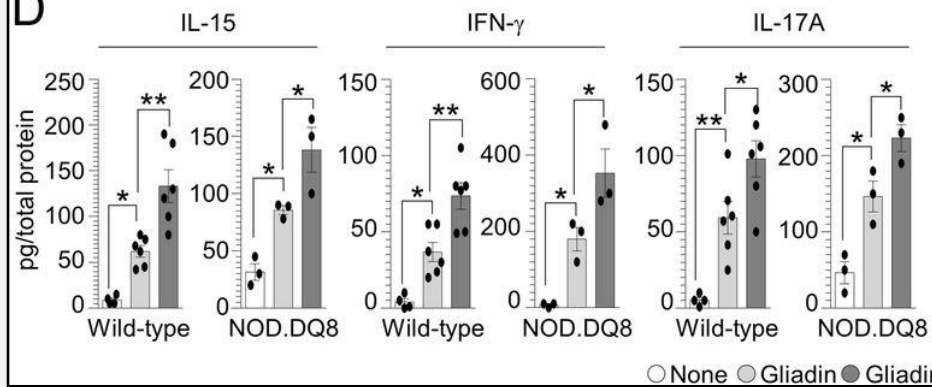
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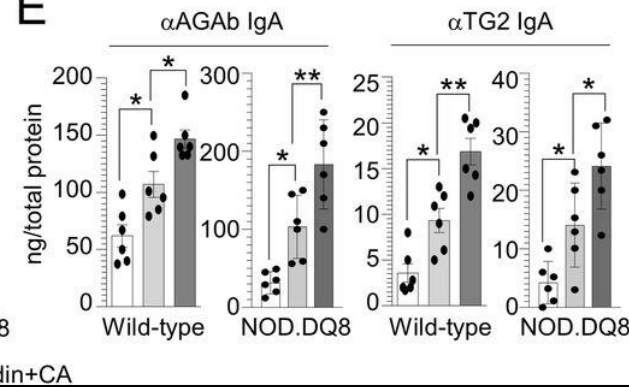
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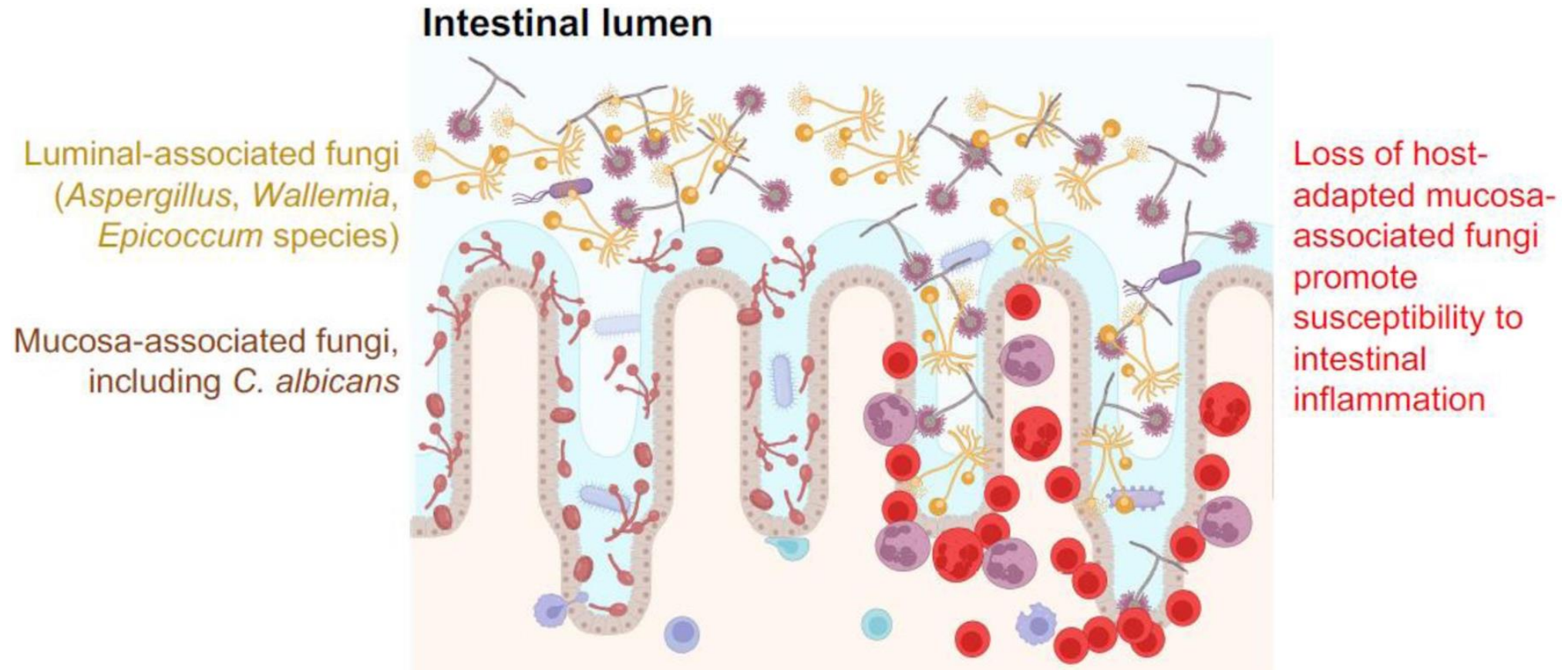


E

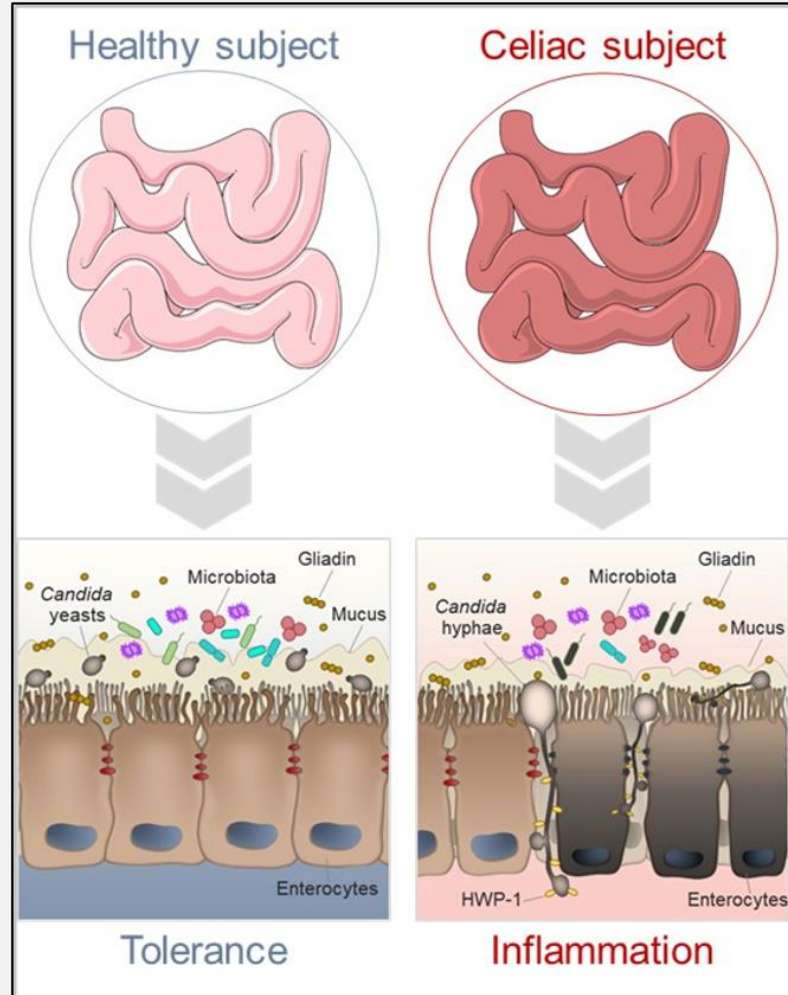


*Candida albicans*  
exacerbates  
intestinal  
pathology in  
gluten-  
sensitized  
mice

*C. albicans* and other fungal species lie in close approximation with the intestinal mucosa, whereas other fungi including *Aspergillus*, *Wallemia*, and *Epicoccum* species are more restricted to the intestinal lumen. Fluconazole promotes susceptibility to intestinal inflammation



# Studio della interazione tra i mastociti e *Candida albicans* nello sviluppo della celiachia

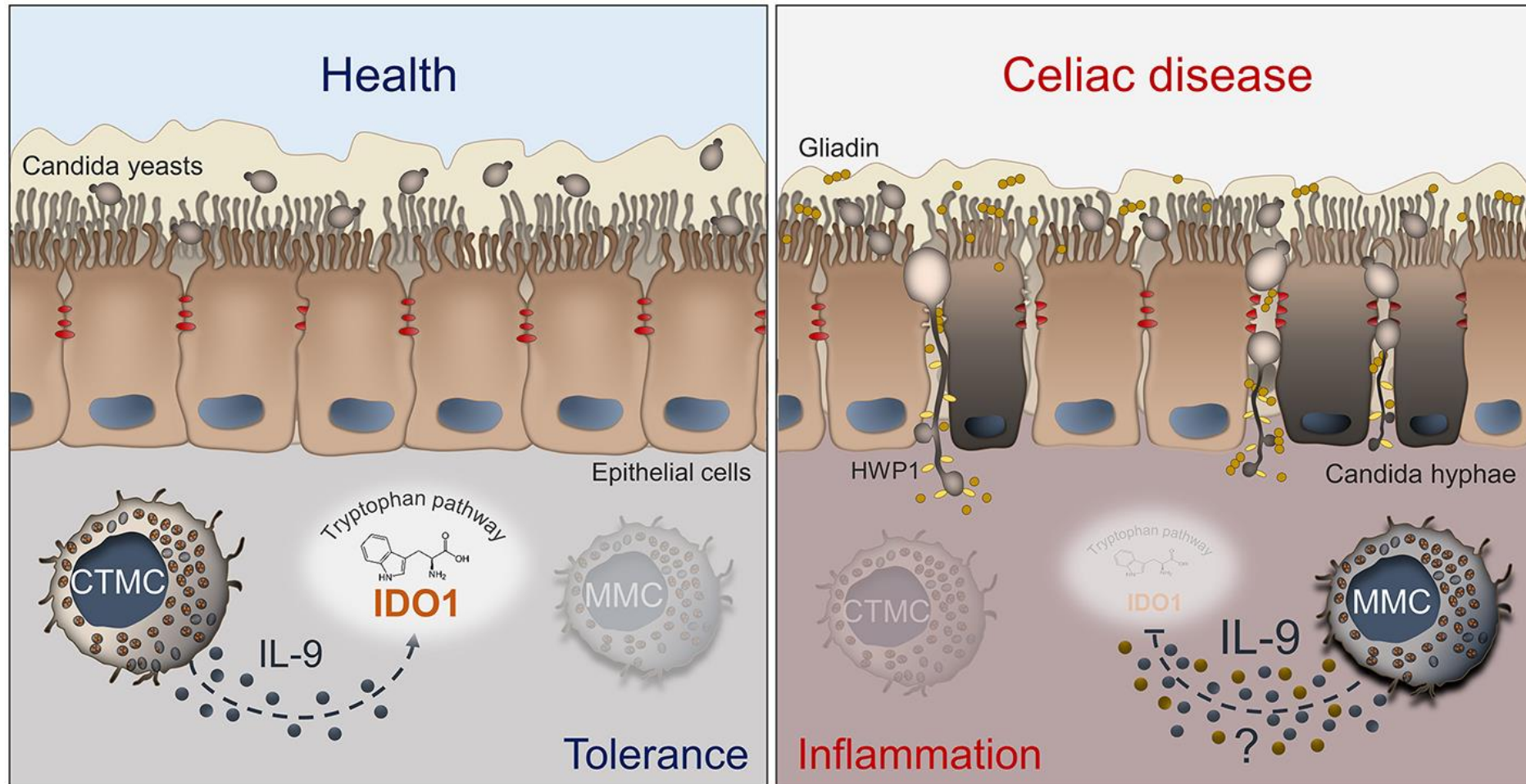


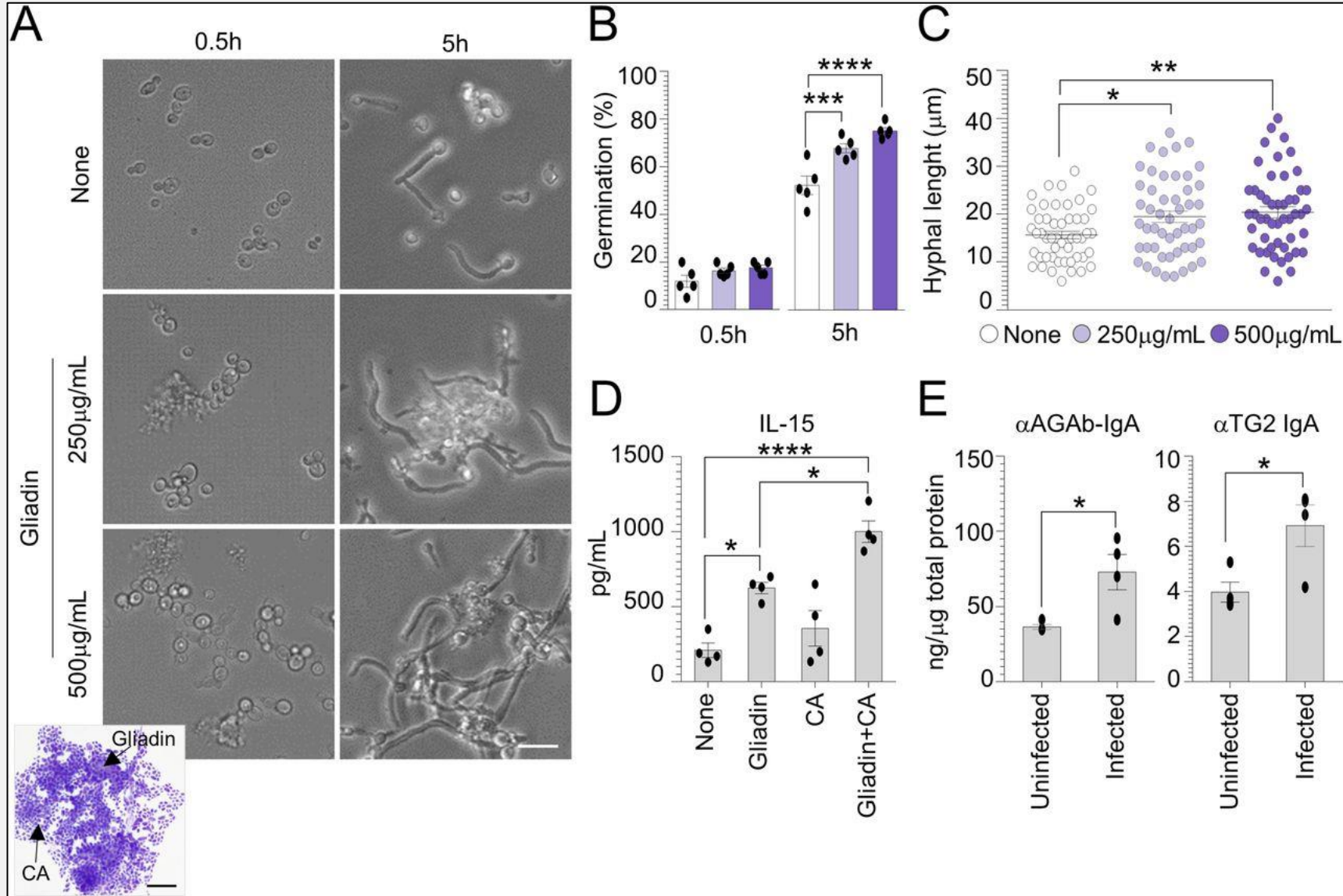
FC 008/2018

**The immune and microbial  
homeostasis determines the  
*Candida*-mast cells cross-talk  
in celiac disease**

Life Science Alliance May  
2024, 7 (7) e202302441

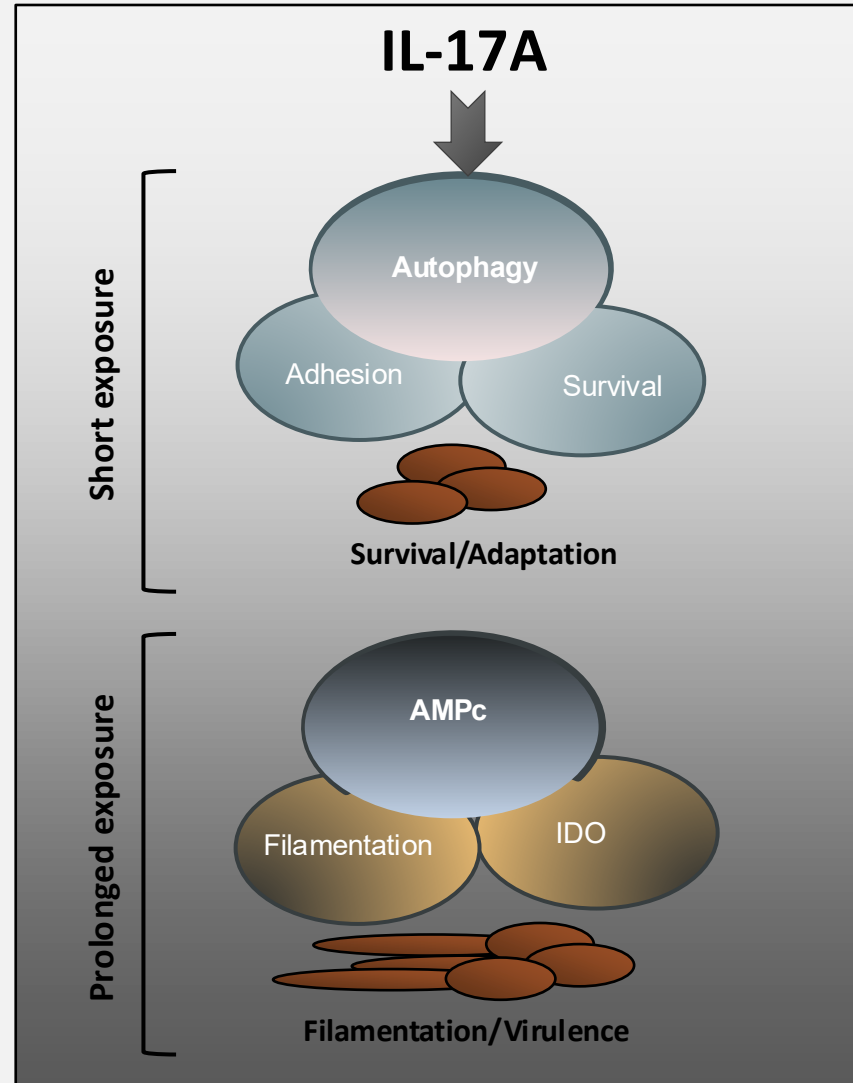
# *Candida albicans* and Celiac Disease: To Be or Not to Be a Pathogen?





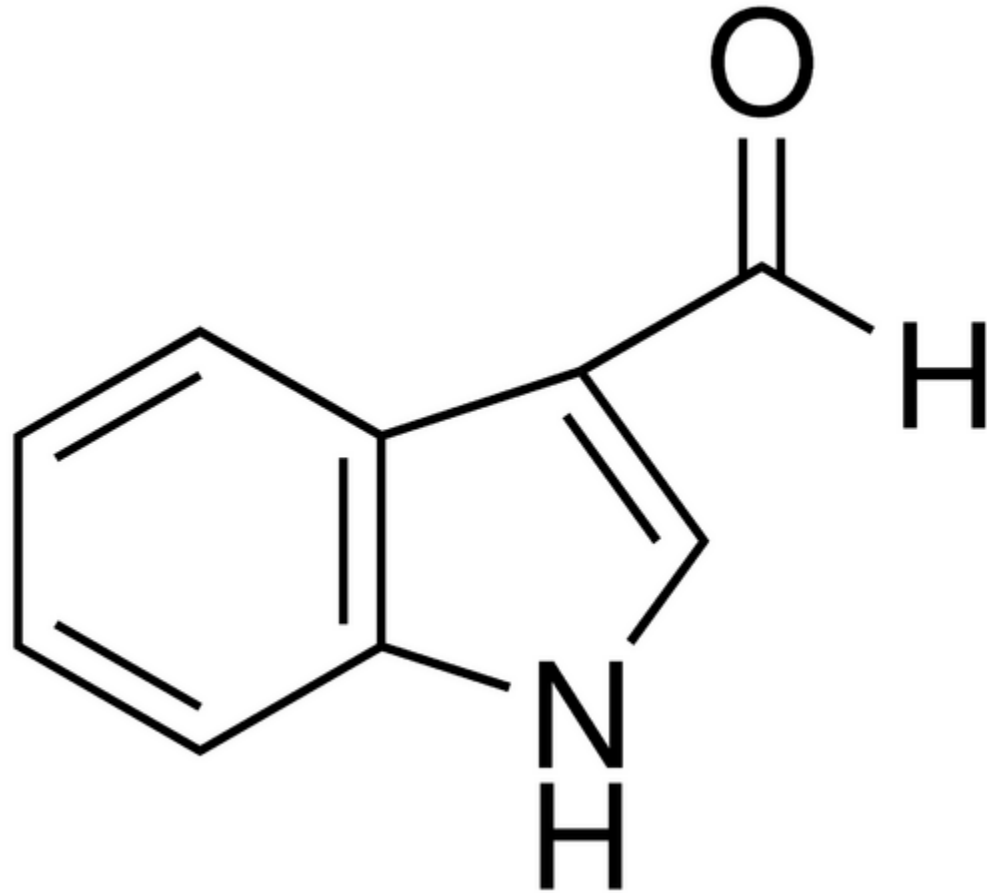
Gliadin  
peptides  
affect  
*C. albicans*  
morphotype

# Inflammation may promote fungal growth and virulence



# IL POSTBIOTICO

## Indole-3-Aldehyde

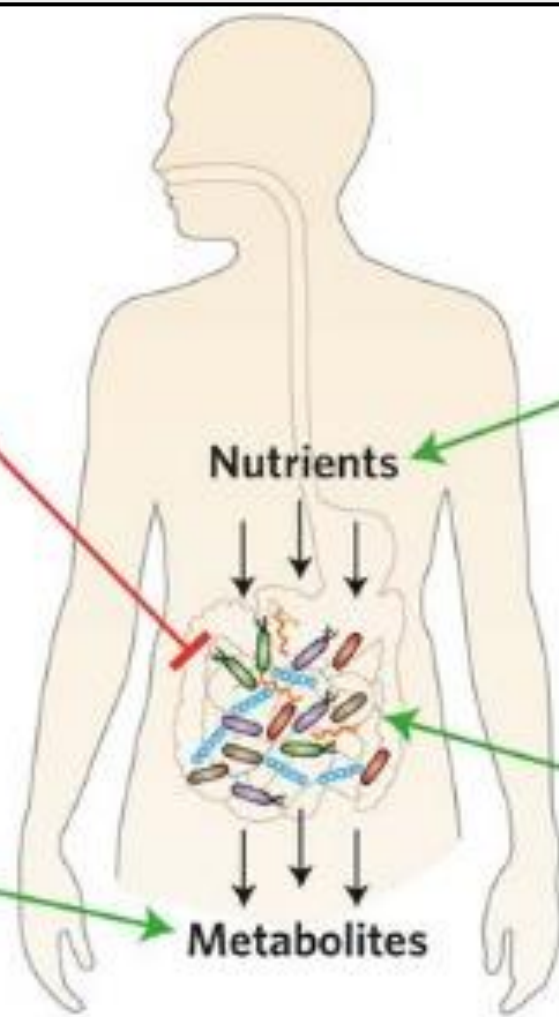


### Antibiotics

- Gut decontamination
- Rifaximin
- Commensal-sparing regimens
- Timing of initiation or discontinuation of prophylactic and empiric-fever treatments

### Postbiotics

- Short-chain fatty acids (e.g. butyrate)
- Indole derivatives
- Avoidance of foods that compromise mucus barrier



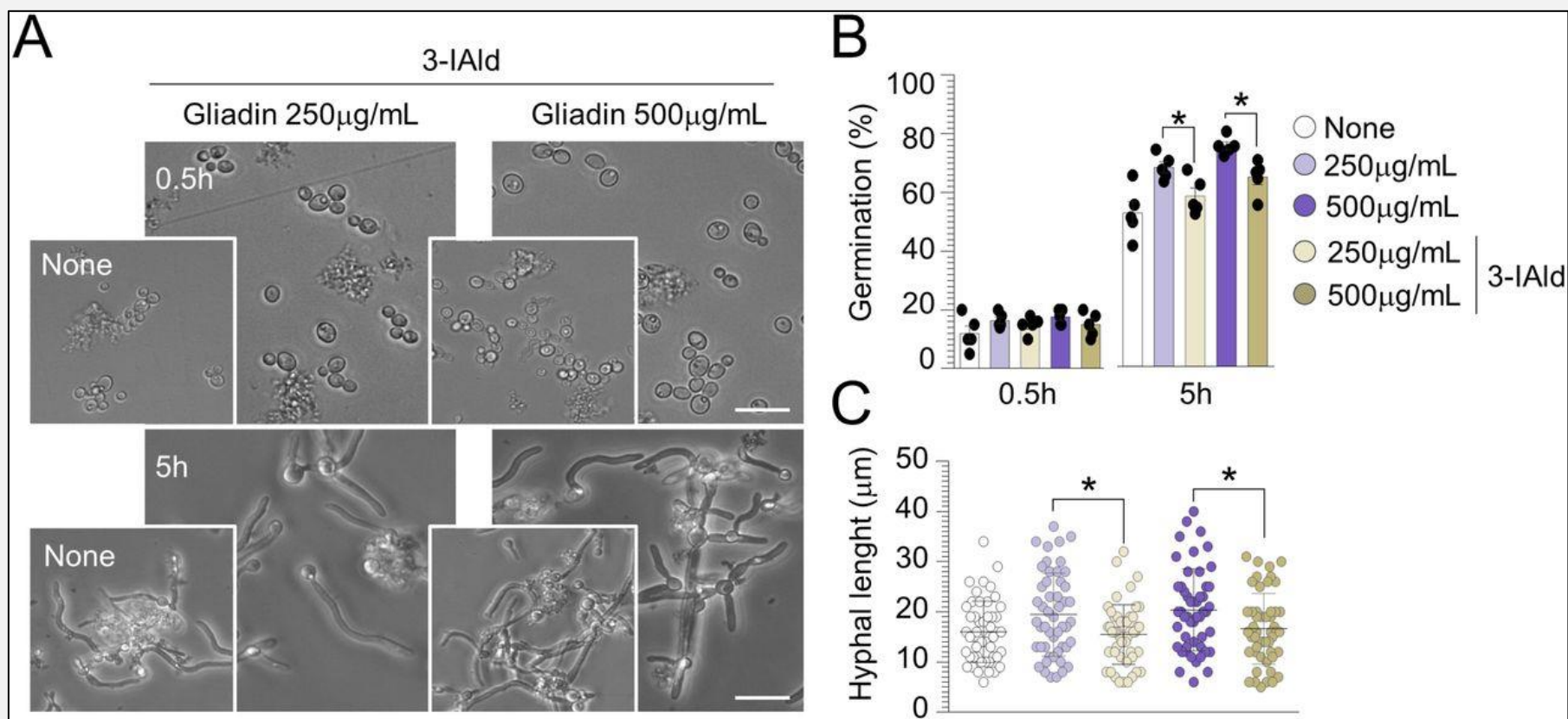
### Prebiotics

- Non-digestible carbohydrates
- Avoidance or encouragement of certain foods

### Probiotics

- Faecal transplant
- Engineered microbes
- Rationally selected strains

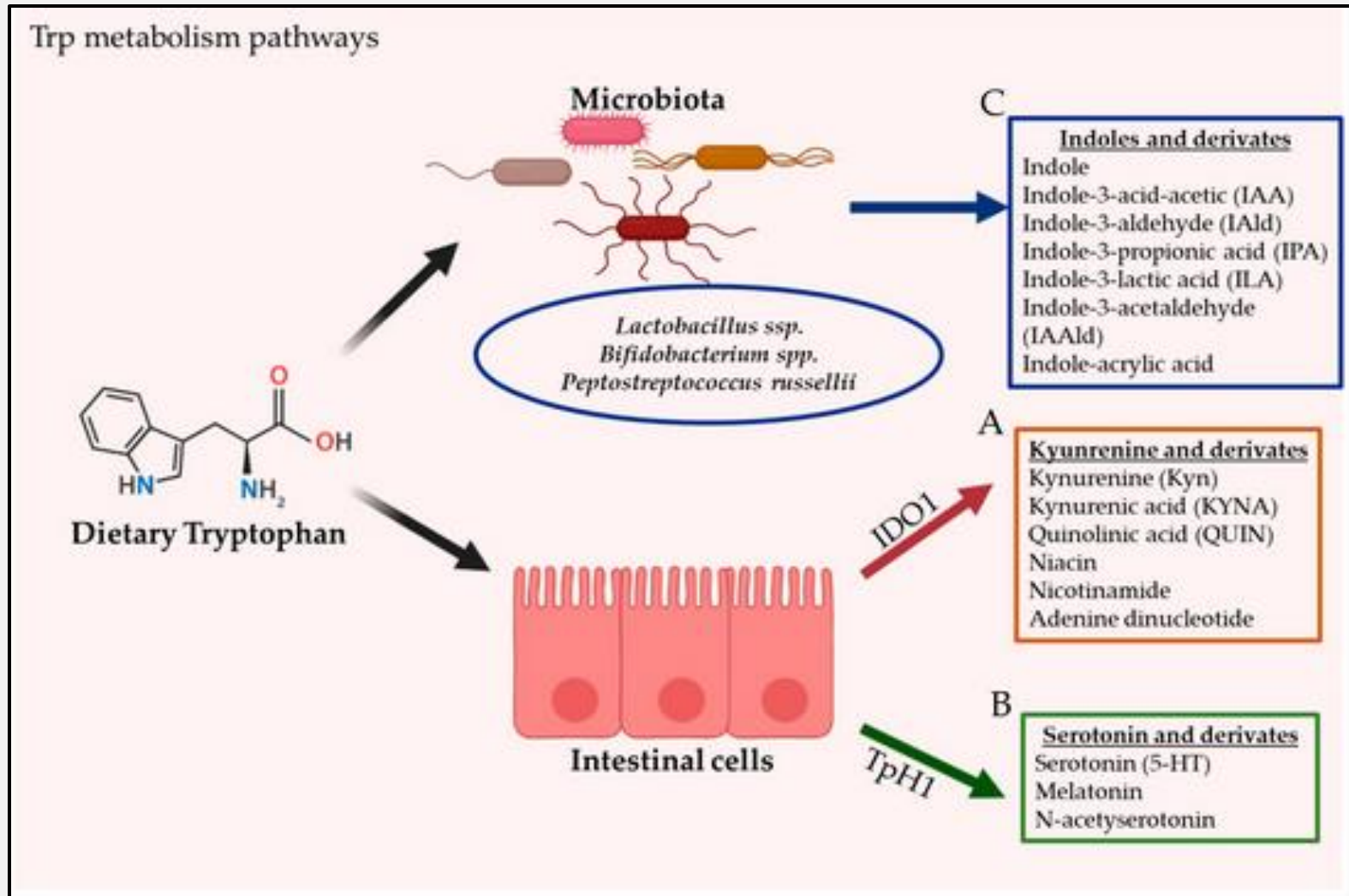
# 3-IAld antagonizes the gliadin-induced fungal filamentation

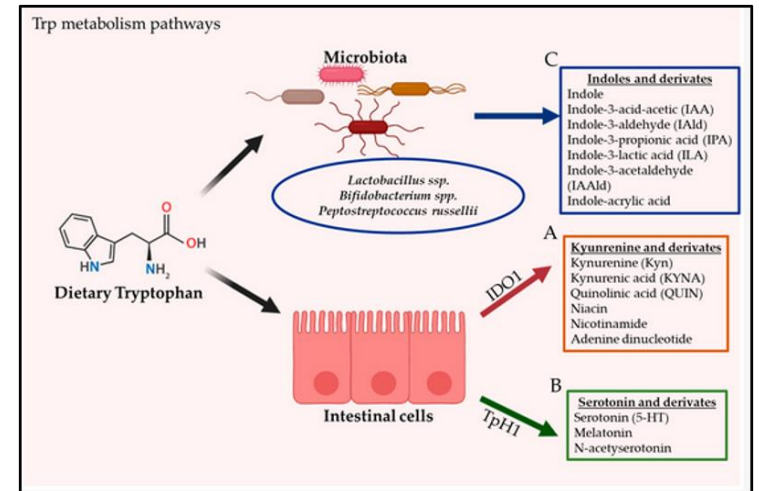
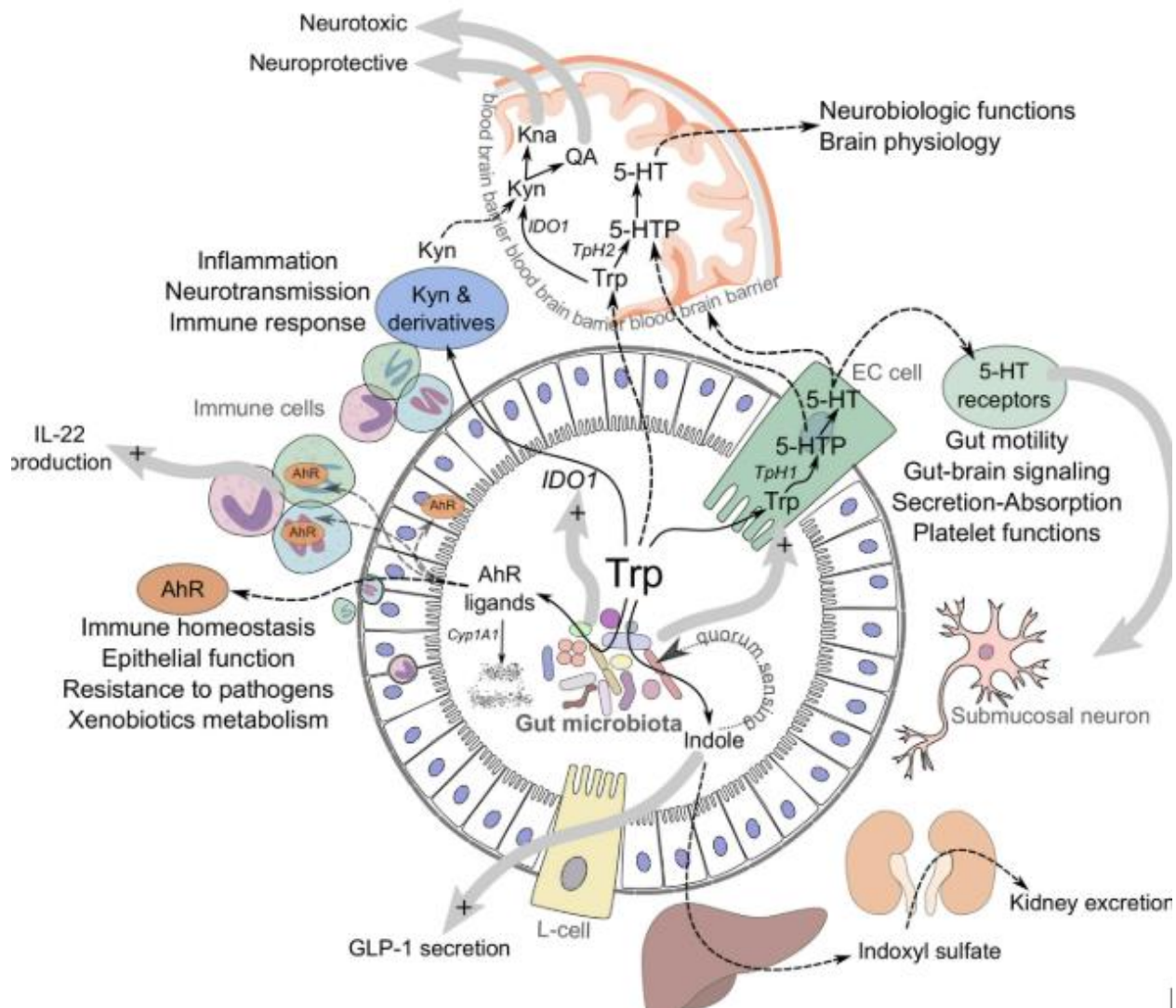


# Postbiotics: next-generation microbiome therapeutics

- ISAPP 2021 consensus definition: preparations of inanimate microorganisms and/or their components conferring health benefits.
- Include peptides, exopolysaccharides, cell wall fragments and microbial metabolites.
- Potential advantages: safety, stability, reproducibility and easier industrial standardization.

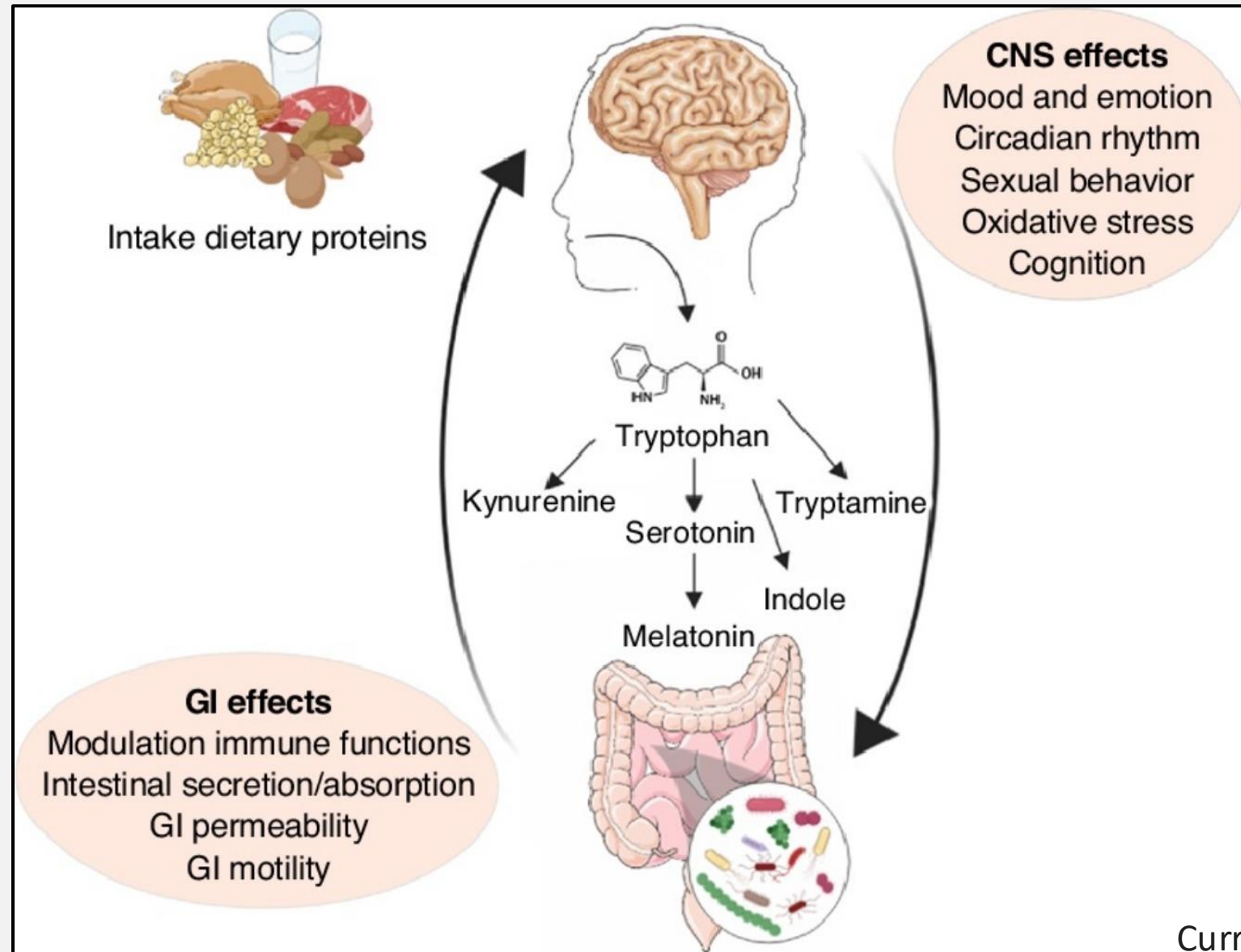
# Tryptophan partitioning at mucosal surfaces





### Tryptophan partitioning at mucosal surfaces

# Tryptophan metabolism and the microbiome-gut-brain axis



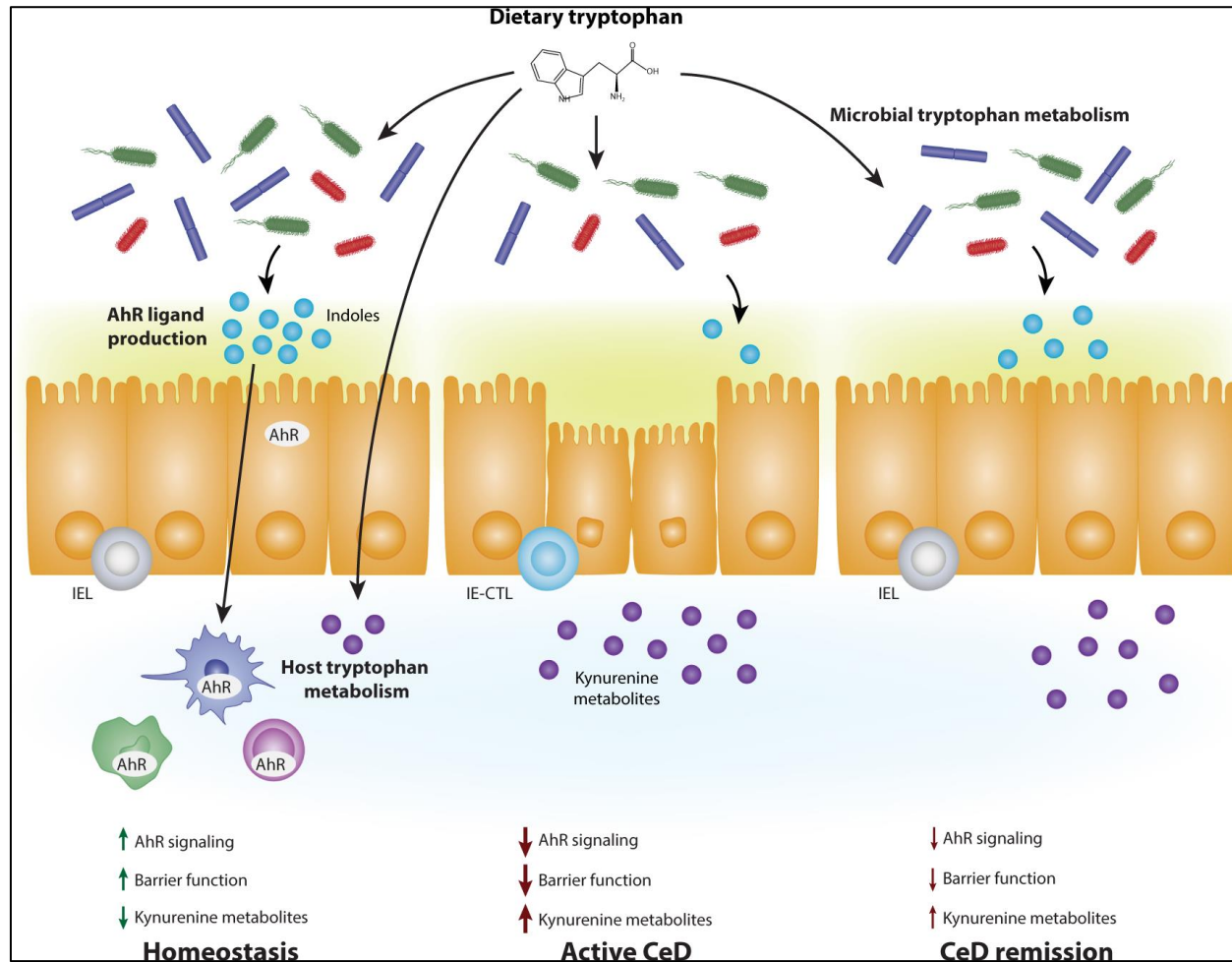
## CELIAC DISEASE

# Aryl hydrocarbon receptor ligand production by the gut microbiota is decreased in celiac disease leading to intestinal inflammation

Bruno Lamas<sup>1\*</sup>, Leticia Hernandez-Galan<sup>1\*</sup>, Heather J. Gallipeau<sup>1</sup>, Marco Constante<sup>1</sup>, Alexandra Clarizio<sup>1</sup>, Jennifer Jury<sup>1</sup>, Natalia M. Breyner<sup>1</sup>, Alberto Camlnero<sup>1</sup>, Gaston Rueda<sup>1</sup>, Christina L. Hayes<sup>1</sup>, Justin L. McCarville<sup>1</sup>, Miriam Bermudez Brito<sup>1</sup>, Julien Planchals<sup>2</sup>, Nathalie Rolhion<sup>3</sup>, Joseph A. Murray<sup>4</sup>, Philippe Langella<sup>2</sup>, Linda M. P. Loonen<sup>5</sup>, Jerry M. Wells<sup>5</sup>, Premysl Bercik<sup>1</sup>, Harry Sokol<sup>2,3†‡</sup>, Elena F. Verdu<sup>1†‡</sup>

Metabolism of tryptophan by the gut microbiota into derivatives that activate the aryl hydrocarbon receptor (AhR) contributes to intestinal homeostasis. Many chronic inflammatory conditions, including celiac disease involving a loss of tolerance to dietary gluten, are influenced by cues from the gut microbiota. We investigated whether AhR ligand production by the gut microbiota could influence gluten immunopathology in nonobese diabetic (NOD) mice expressing DQ8, a celiac disease susceptibility gene. NOD/DQ8 mice, exposed or not exposed to gluten, were subjected to three interventions directed at enhancing AhR pathway activation. These included a high-tryptophan diet, gavage with *Lactobacillus reuteri* that produces AhR ligands or treatment with an AhR agonist. We investigated intestinal permeability, gut microbiota composition determined by 16S rRNA gene sequencing, AhR pathway activation in intestinal contents, and small intestinal pathology and inflammatory markers. In NOD/DQ8 mice, a high-tryptophan diet modulated gut microbiota composition and enhanced AhR ligand production. AhR pathway activation by an enriched tryptophan diet, treatment with the AhR ligand producer *L. reuteri*, or pharmacological stimulation using 6-formylindolo (3,2-b) carbazole (Fic2) decreased immunopathology in NOD/DQ8 mice exposed to gluten. We then determined AhR ligand production by the fecal microbiota and AhR activation in patients with active celiac disease compared to nonceliac control individuals. Patients with active celiac disease demonstrated reduced AhR ligand production and lower intestinal AhR pathway activation. These results highlight gut microbiota-dependent modulation of the AhR pathway in celiac disease and suggest a new therapeutic strategy for treating this disorder.

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of Science. No claim  
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Government Works



- Active CeD has impaired capacity to metabolize tryptophan to AhR ligands, and tryptophan metabolism is shifted to the kynurenine pathway which is implicated in inflammatory diseases.
- The impaired tryptophan metabolism is partially restored in CeD patients after 2-years on a gluten-free diet (GFD), resulting in reduced kynurenine metabolites and increased microbiota-dependent AhR ligands.

## *Saccharomyces boulardii* CNCM I-745 synergizes with the small intestinal microbiota to boost AhR signaling in celiac disease

Kelly R. Kan<sup>a,b,1</sup>, Marco Constante<sup>a,1</sup>, Sara Rahmani<sup>a,c</sup>, Gaston H. Rueda<sup>a</sup>, Mark Wulczynski<sup>a</sup>, Maria Ines Pinto-Sanchez<sup>a</sup>, Xavier Roux<sup>d</sup>, Premysl Bercik<sup>a</sup>, Heather J. Galipeau<sup>a</sup>, Alberto Caminero<sup>a</sup> and Elena F. Verdu<sup>a,b</sup>

<sup>a</sup>Department of Medicine, Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, Ontario, Canada; <sup>b</sup>Department of Biochemistry and Biomedical Sciences, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada; <sup>c</sup>School of Biomedical Engineering, McMaster University, Hamilton, Ontario, Canada; <sup>d</sup>Microbiology Department, Blocodex, 3 Chemin d'Armancourt, Compiègne, France

### ABSTRACT

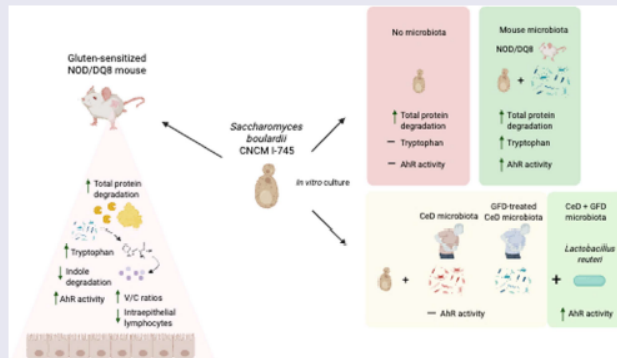
Celiac disease (CeD) is an immune-mediated condition that leads to small intestinal villous atrophy and is driven by dietary gluten in individuals carrying HLA-DQ2 and DQ8. Microbial factors have been implicated in both the onset of CeD and persistent symptoms (non-responsive CeD) after the gluten-free diet (GFD), through mechanisms including impaired tryptophan metabolism and aryl hydrocarbon receptor (AhR) pathway activation. Although probiotics have been shown to be safe in CeD, there are currently no clinical recommendations for strains that target disease-related mechanisms. We here demonstrate that *S. boulardii* activated the AhR pathway in gluten-sensitized mice expressing HLA-DQ8, improving gluten-immunopathology. Mechanistically, *S. boulardii* enhanced the CeD patients' microbiota capacity for AhR activation when duodenal indole-producing commensals, such as *Lactobacillus reuteri*, were present. Our study provides preclinical evidence that *S. boulardii* CNCM I-745 targets a microbial deficiency previously described in CeD through modulation of microbial tryptophan metabolism. The findings encourage clinical testing of *S. boulardii* in CeD to prevent or better treat non-responsive cases.

### ARTICLE HISTORY

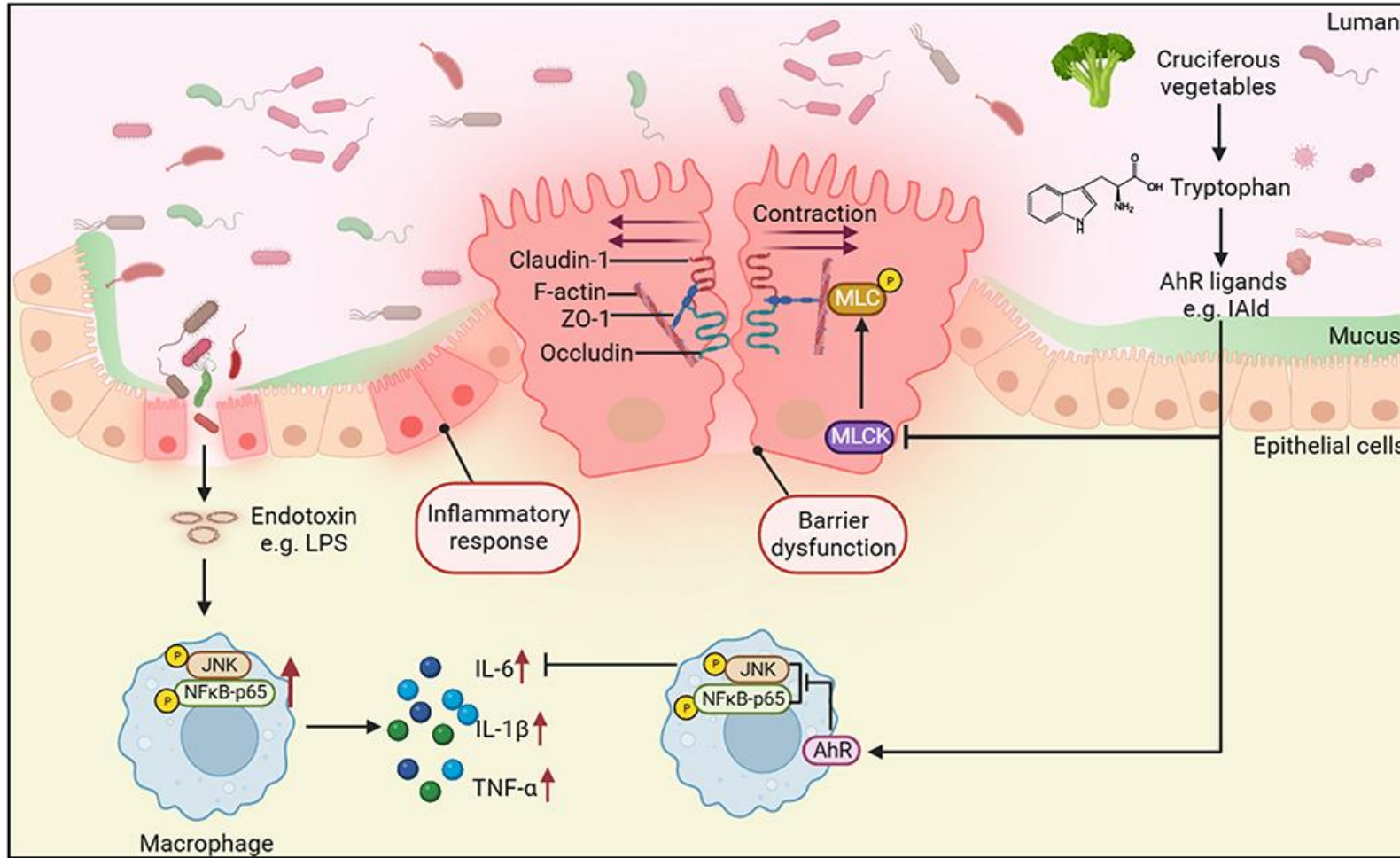
Received 26 August 2025  
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Accepted 21 April 2026

### KEYWORDS

Celiac disease;  
*Saccharomyces boulardii*; aryl  
hydrocarbon receptor (AhR);  
tryptophan metabolism;  
protein degradation;  
probiotics



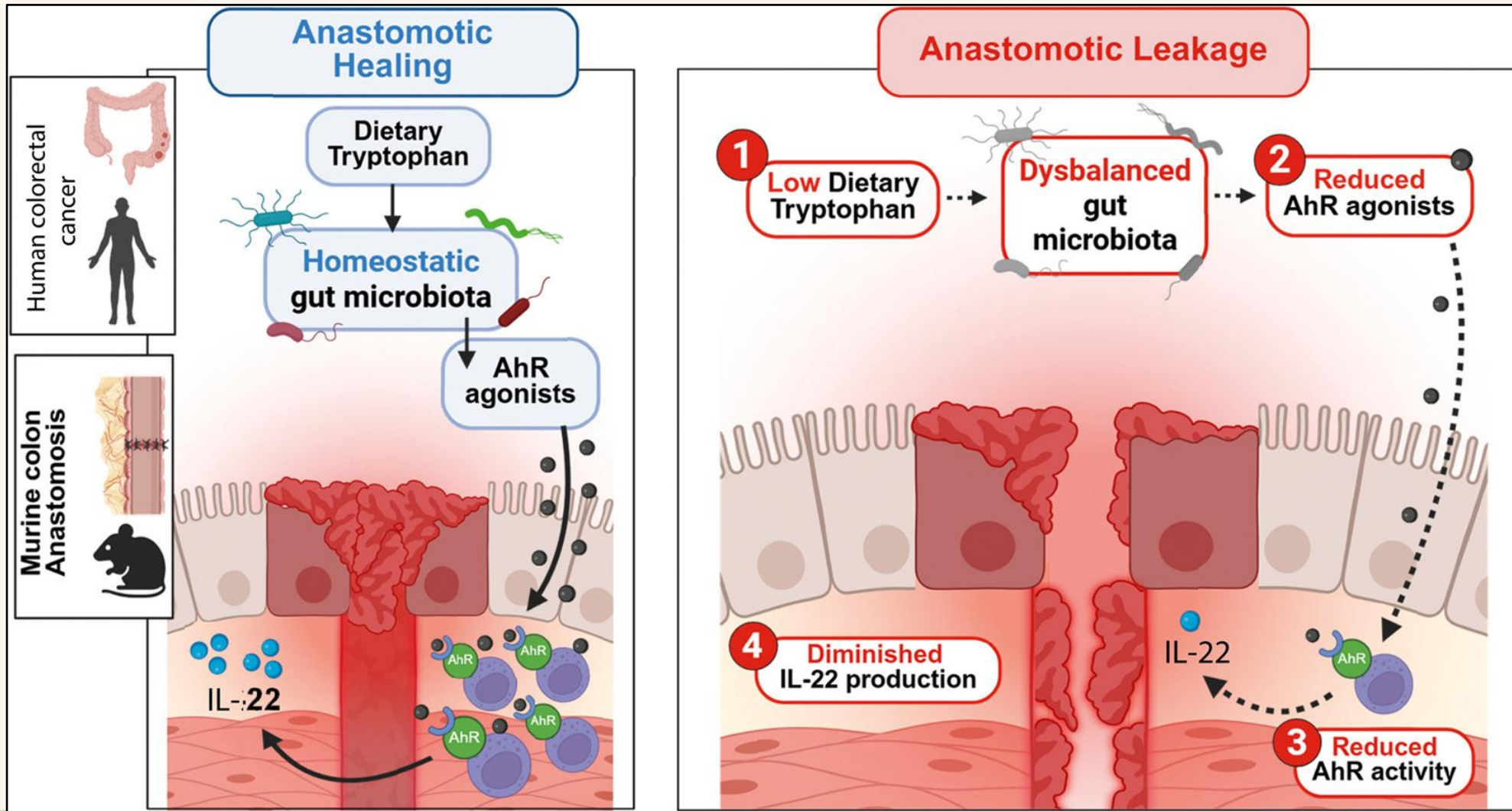
.....Our study provides preclinical evidence that *S. boulardii* CNCM I-745 targets a microbial deficiency previously described in CeD through modulation of microbial tryptophan metabolism



Indole-3-Aldehyde  
Reduces  
Inflammatory  
Responses and  
Restores  
Intestinal  
Epithelial Barrier  
Function Partially  
via Aryl  
Hydrocarbon  
Receptor (AhR) in  
Experimental  
Colitis Models

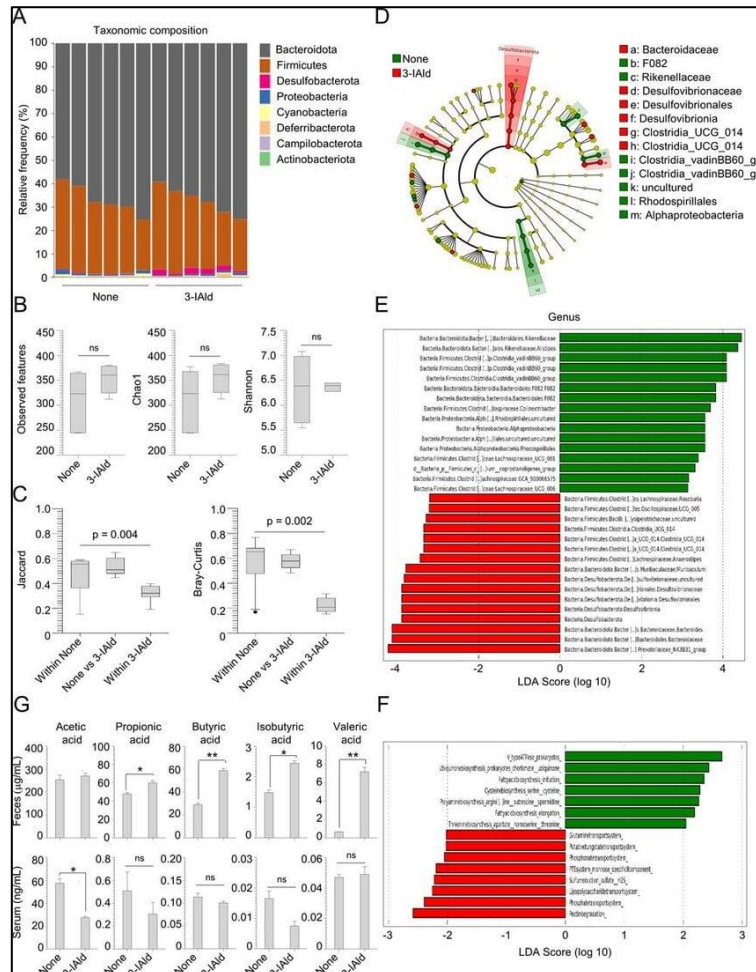
*J. Infl Res 2024*

# IL-22, il santo protettore degli epiteli

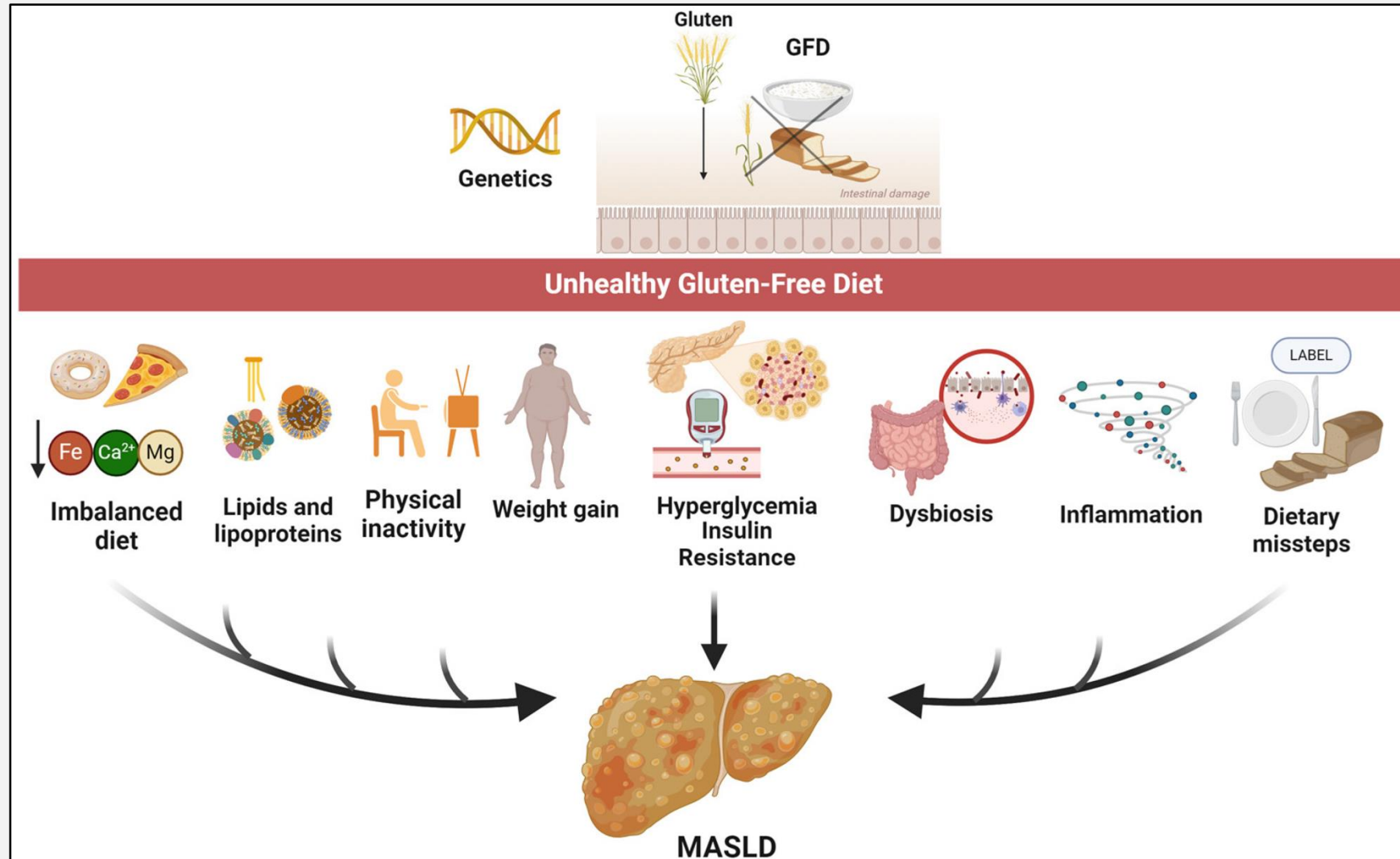


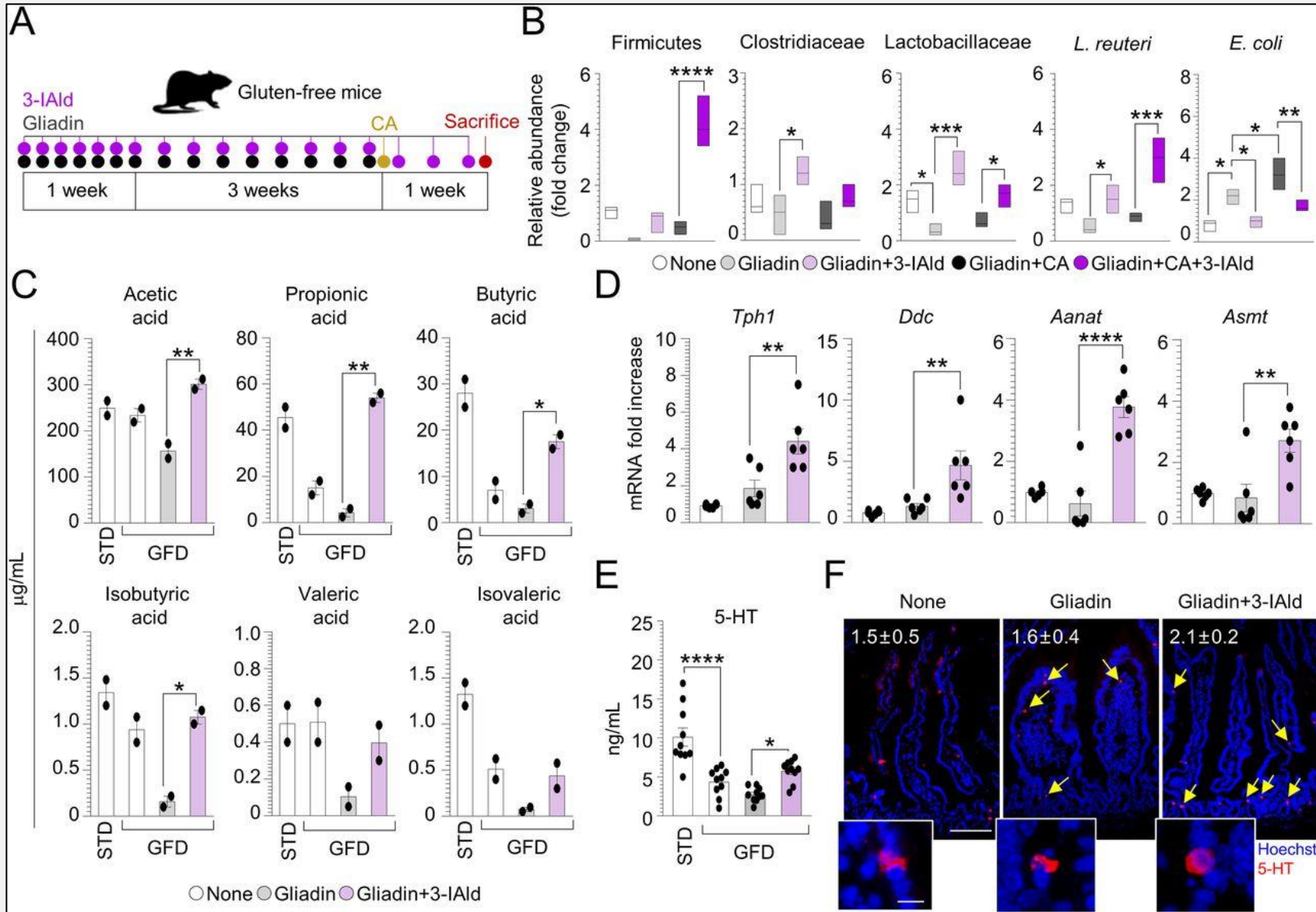
# 3-IAld modifies intestinal microbiota composition and function

Journal for ImmunoTherapy of Cancer 2024

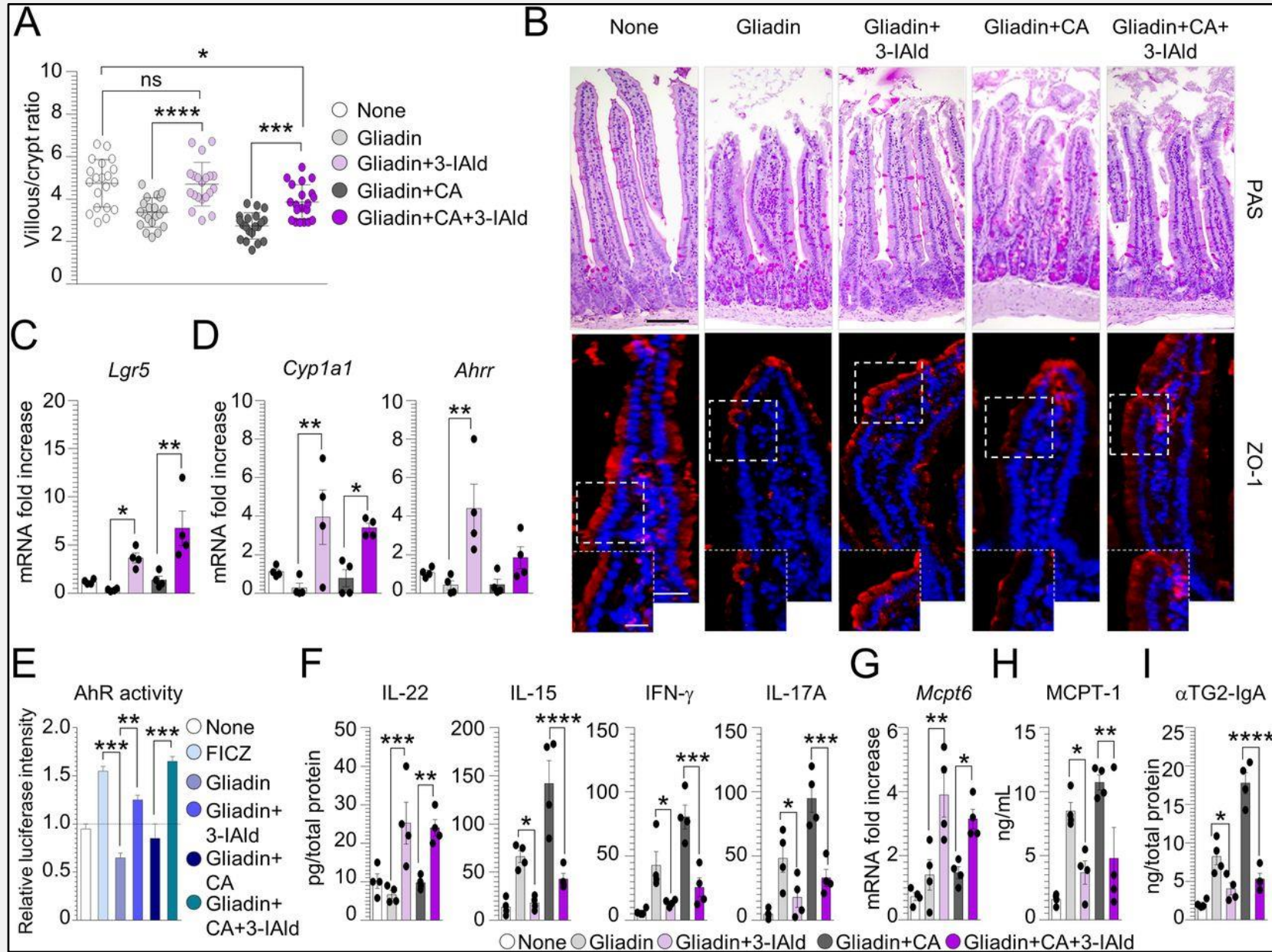


# Patients with Celiac Disease Have High Prevalence of Fatty Liver and Metabolic Syndrome





Indole-3-  
aldehyde  
modulates  
microbiota  
composition  
and  
metabolic  
profile in  
celiac  
disease

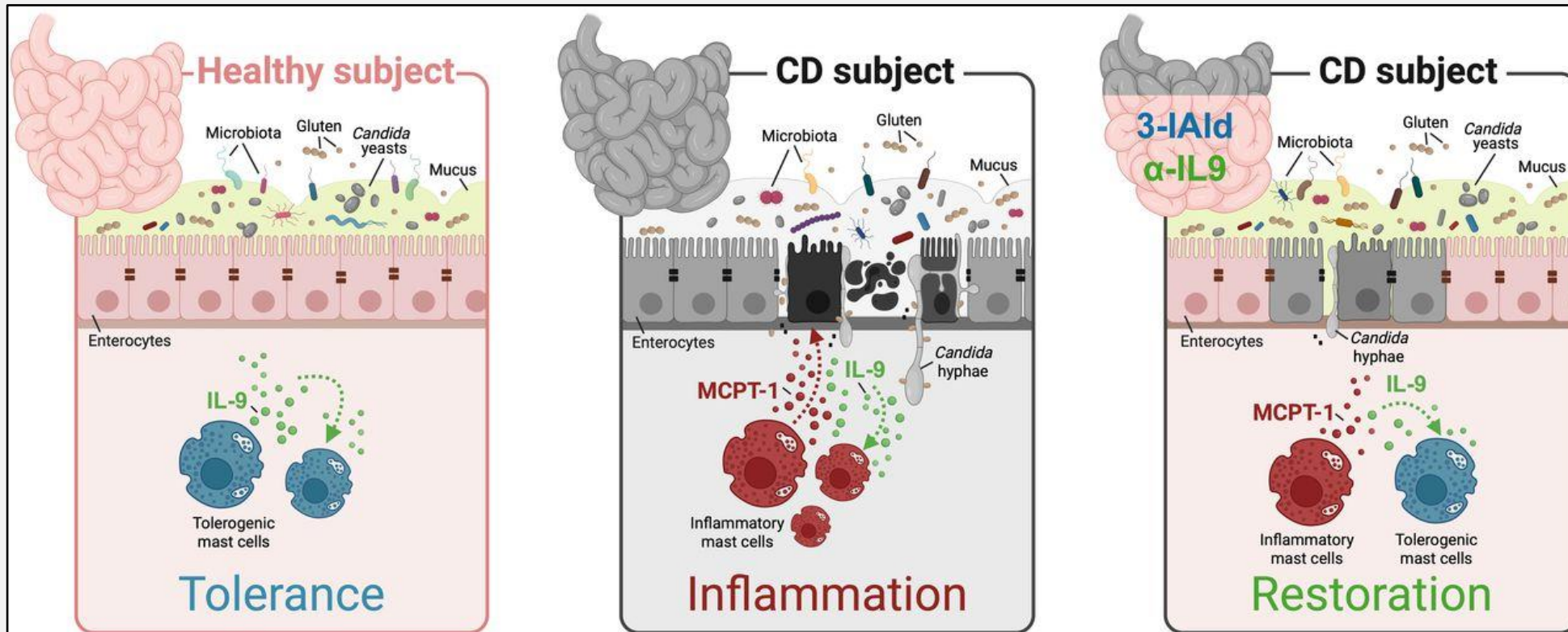


Indole-3-  
aldehyde  
protects  
from celiac  
disease  
intestinal  
pathology

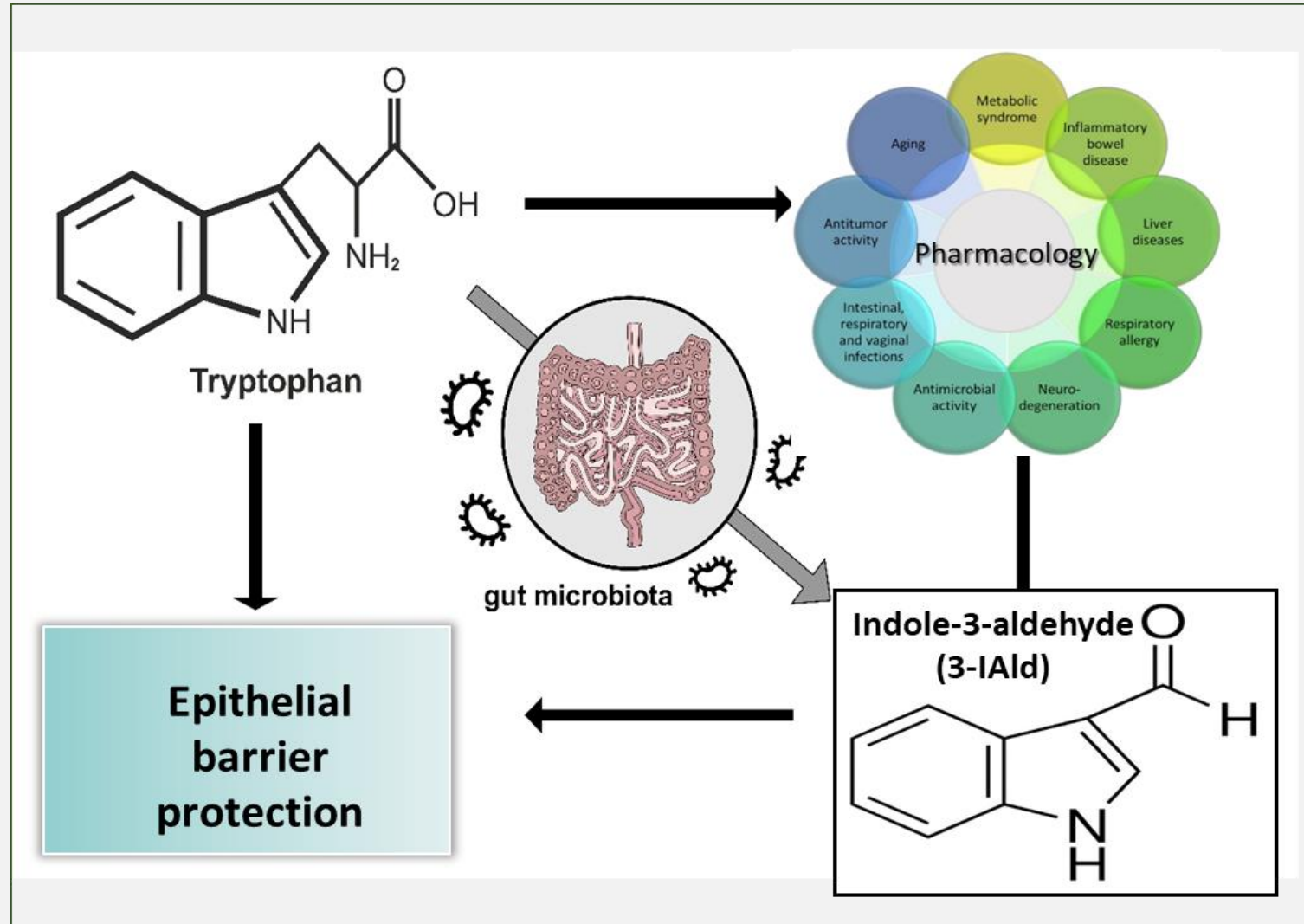
FC 008/2018

# The immune and microbial homeostasis determines the *Candida*-mast cells cross-talk in celiac disease

Life Science Alliance May  
2024, 7 (7) e202302441



# 3-IAld's therapeutics: Orfan Drug Designation!



# Why Metagenomics IS Not Enough

**Table 4.**  
Microbiome composition described in reviewed publications, regarding the former phyla *Firmicutes*, *Actinobacteria*, *Bacteroidetes*, *Proteobacteria*, *Fusobacteria*, and *Verrucomicrobia*.

| articles                               | Firmicutes              | Bacteroidetes           | Fusobacteria         | Proteobacteria  | Verrucomicrobia | Actinobacteria       | Bacteroides          | Lactobacillus        | Other groups |
|----------------------------------------|-------------------------|-------------------------|----------------------|-----------------|-----------------|----------------------|----------------------|----------------------|--------------|
| Newborns                               |                         |                         |                      |                 |                 |                      |                      |                      |              |
| Nivares et al. (24)                    | -                       | -                       | -                    | -               | -               | -                    | -                    | -                    | S            |
| Newborns and children                  |                         |                         |                      |                 |                 |                      |                      |                      |              |
| ellitto et al. <sup>2</sup> (10)       | HA overall              | HA controls             | -                    | -               | -               | HA overall           | Present              | HA overall           | S, G, P      |
| Nivares et al. (25)                    | Present <sup>b</sup>    | Present                 | -                    | Present         | -               | Present              | -                    | -                    | S, G, P      |
| Leonard et al. (26)                    | Present                 | Present                 | -                    | -               | -               | -                    | -                    | -                    | S, G         |
| Leonard et al. (27)                    | -                       | -                       | -                    | -               | -               | -                    | -                    | -                    | -            |
| Children                               |                         |                         |                      |                 |                 |                      |                      |                      |              |
| Barbato et al. <sup>2</sup> (8)        | -                       | -                       | -                    | -               | -               | -                    | -                    | -                    | -            |
| Yu et al. (28)                         | Present                 | Present                 | Present              | LA              | -               | HA overall           | -                    | -                    | S, G, P      |
| Meij et al. (29)                       | Present                 | Present                 | -                    | -               | -               | Present              | HA                   | HA overall           | S, G, P      |
| Pozo-Rubio et al. (30)                 | -                       | -                       | -                    | -               | -               | -                    | Present              | Present              | S, G         |
| DiGirolamo et al. (18)                 | Present                 | LA <sup>b</sup>         | -                    | Present         | Present         | LA <sup>b</sup>      | Present              | Present              | S, G, P      |
| Almouzni and Boutrid <sup>2</sup> (15) | -                       | -                       | -                    | -               | -               | -                    | -                    | -                    | -            |
| Antala et al. (22)                     | -                       | -                       | -                    | -               | -               | -                    | Present              | Present              | G, P         |
| Asfropoulou et al. (17)                | Present                 | -                       | -                    | -               | -               | LA                   | Present <sup>b</sup> | Present <sup>b</sup> | S, G, P      |
| Ample et al. (31)                      | -                       | -                       | -                    | -               | -               | -                    | Present <sup>b</sup> | Present              | S, G         |
| Leonard et al. (16)                    | -                       | -                       | -                    | -               | -               | -                    | LA <sup>b</sup>      | -                    | S, G         |
| Ingh et al. (32)                       | Present                 | HA                      | -                    | HA <sup>b</sup> | Present         | HA overall           | -                    | -                    | G, P         |
| Blase et al. (33)                      | -                       | HA <sup>b</sup>         | -                    | HA              | -               | -                    | LA <sup>b</sup>      | -                    | G, P         |
| Fouzan et al. (34)                     | HA overall <sup>b</sup> | HA overall <sup>b</sup> | -                    | HA overall      | HA overall      | LA                   | LA                   | HA <sup>b</sup>      | S, G, P      |
| Filletich et al. (35)                  | -                       | -                       | -                    | -               | -               | -                    | Present              | -                    | G            |
| Fouzan et al. (36)                     | -                       | -                       | -                    | LA              | -               | -                    | LA                   | -                    | S            |
| Guayo-Patón et al. (37)                | Present                 | Present                 | -                    | HA overall      | Present         | Present              | Present              | -                    | G, P         |
| Jirathar et al. (38)                   | -                       | -                       | -                    | -               | -               | -                    | Present              | -                    | S, G, P      |
| Adults                                 |                         |                         |                      |                 |                 |                      |                      |                      |              |
| Natal et al. (39)                      | HA overall              | -                       | Present              | HA overall      | -               | HA overall           | -                    | HA overall           | G, P         |
| García-Mascardo et al. (40)            | HA overall              | LA overall <sup>b</sup> | LA <sup>b</sup>      | Present         | -               | HA overall           | -                    | -                    | G, P         |
| Podkhe et al. (41)                     | Present <sup>b</sup>    | Present <sup>b</sup>    | -                    | Present         | -               | Present              | Present              | Present              | S, G, P      |
| Erera et al. (42)                      | Present                 | HA overall              | -                    | HA overall      | -               | HA overall           | Present              | -                    | G, P         |
| Rancavilla et al. (19)                 | -                       | -                       | -                    | -               | -               | Present              | -                    | Present              | S, G, P      |
| Sanelli et al. (43)                    | LA <sup>b</sup>         | Present <sup>b</sup>    | Present <sup>b</sup> | HA <sup>b</sup> | -               | LA                   | HA                   | -                    | S, G, P      |
| Rylund et al. (44)                     | -                       | -                       | -                    | -               | -               | Present              | -                    | -                    | S, G, P      |
| Mecol et al. (20)                      | -                       | -                       | -                    | -               | -               | -                    | -                    | -                    | S, G         |
| Abbó et al. (45)                       | Present <sup>b</sup>    | Present                 | -                    | Present         | Present         | Present <sup>b</sup> | LA <sup>b</sup>      | -                    | G, P         |
| Basari et al. (46)                     | HA <sup>b</sup>         | Present                 | -                    | -               | -               | Present              | -                    | LA overall           | G, P         |
| Jobel et al. (47)                      | LA                      | HA                      | -                    | HA              | -               | -                    | -                    | -                    | P            |
| Chieppati et al. (48)                  | LA <sup>b</sup>         | -                       | -                    | Present         | -               | Present              | -                    | -                    | G, P         |
| Andrioli et al. (21)                   | -                       | -                       | -                    | Present         | -               | -                    | -                    | Present              | S, G         |
| Constante et al. (49)                  | HA overall <sup>b</sup> | Present <sup>b</sup>    | -                    | -               | -               | -                    | Present <sup>b</sup> | Present              | S, G, P      |
| Hi et al. (23)                         | Present <sup>b</sup>    | HA overall <sup>b</sup> | -                    | HA <sup>b</sup> | -               | HA overall           | -                    | HA <sup>b</sup>      | G, P         |
| Rancavilla et al. (50)                 | LA                      | Present                 | Present              | -               | Present         | Present              | -                    | -                    | S, G, P      |
| Basari et al. (51)                     | HA <sup>b</sup>         | Present <sup>b</sup>    | -                    | -               | -               | -                    | -                    | LA <sup>b</sup>      | G, P         |
| Berfindal et al. (52)                  | HA overall <sup>b</sup> | HA overall              | Present              | HA overall      | -               | Present              | Present              | -                    | G, P         |
| Children and adults                    |                         |                         |                      |                 |                 |                      |                      |                      |              |
| Calliomäki et al. (53)                 | Present                 | -                       | -                    | -               | -               | Present              | Present              | -                    | S, G         |
| Natal et al. (54)                      | Present                 | -                       | HA overall           | HA overall      | -               | HA overall           | -                    | -                    | S, G, P      |
| Sheng et al. (55)                      | -                       | HA overall              | -                    | HA overall      | -               | Present              | Present              | -                    | S, G, P      |
| Sheng <sup>2</sup> (13)                | HA overall              | Present                 | -                    | HA              | -               | HA overall           | Present              | -                    | S, G, P      |
| Age not mentioned                      |                         |                         |                      |                 |                 |                      |                      |                      |              |
| Accioppo et al. <sup>2</sup> (11)      | -                       | -                       | -                    | -               | -               | -                    | -                    | -                    | -            |
| Antierres et al. <sup>2</sup> (9)      | -                       | -                       | -                    | Present         | -               | -                    | -                    | -                    | S            |
| Arroug <sup>2</sup> (12)               | -                       | -                       | -                    | -               | -               | Present              | -                    | -                    | S, G, P      |
| Rylund et al. <sup>2</sup> (14)        | -                       | -                       | -                    | -               | -               | -                    | -                    | -                    | P            |

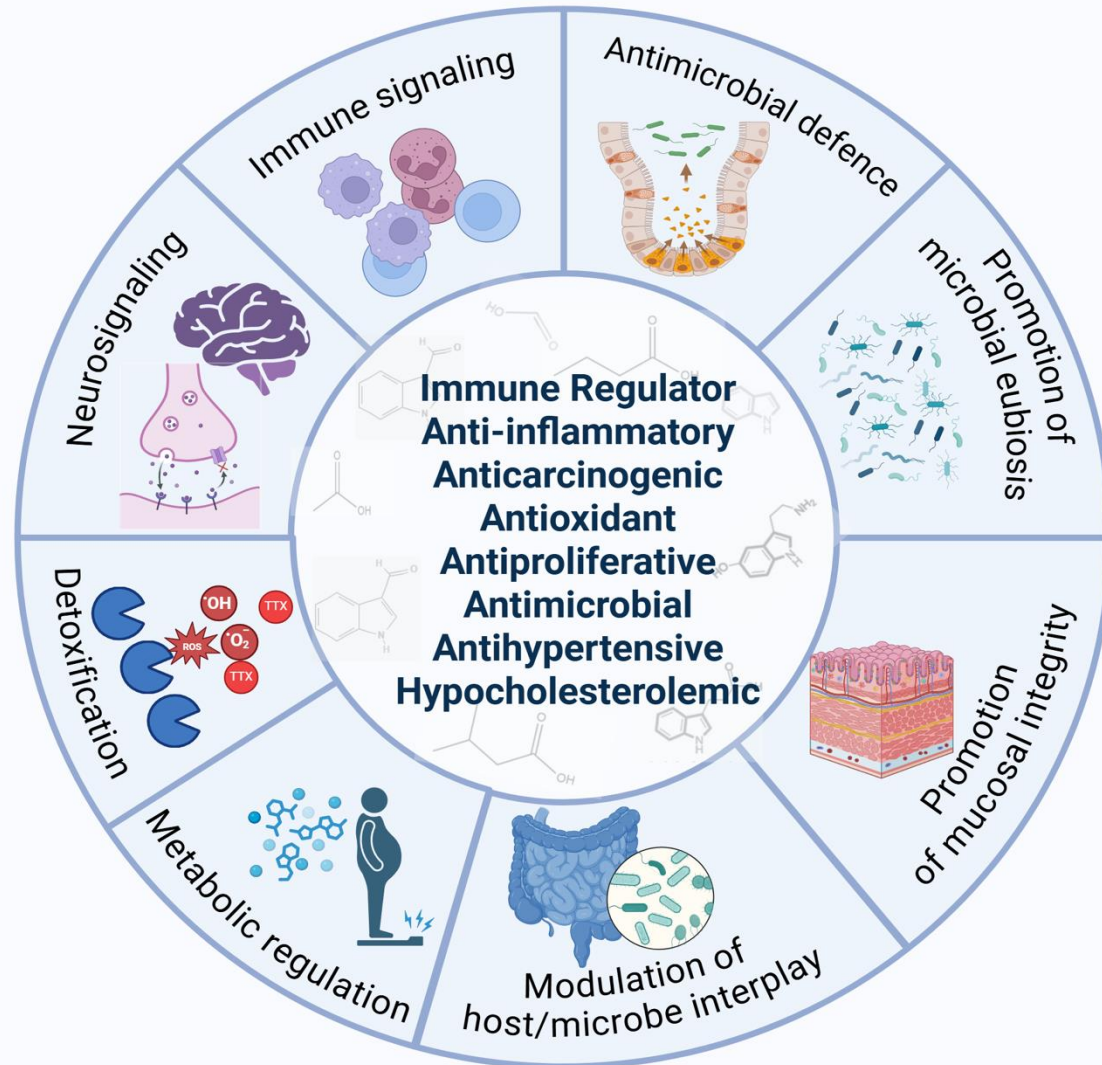
- The review indicates that gut microbiota dysbiosis, marked by altered bacterial composition, contributes significantly to immune-mediated inflammation in celiac disease.
- Researchers suggest that manipulating the microbiome could serve as a future, adjunct treatment alongside a gluten-free diet.

Expert Rev Clin Immunol. 2020

# WHY PROBIOTICS ARE NOT ENOUGH

- Colonization is often transient and strain-dependent.
- Safety concerns may exist in critically ill or immunocompromised patients.
- Need for standardized, stable and mechanism-oriented interventions.

# Why indole postbiotics are promising



# WHY INDOLE POSTBIOTICS ARE PROMISING

The challenge is not to replace a gluten-free diet, but to add metabolic signals that can promote

- epithelial repair
- immunoregulation
- immunometabolism
- microbiota resilience

# Possibili scenari d'impiego

1. Celiaco in GFD con sintomi persistenti: barriera, infiammazione minima, microbiota
2. Fase precoce: accelerare recupero della mucosa insieme a GFD
3. Soggetti a rischio: prevenzione? Solo in studi controllati, con biomarcatori e sicurezza rigorosa
4. Celiaco con fragilità metabolica: GFD e disbiosi possono associarsi a profili metabolici sfavorevoli
5. Disbiosi/candidiasis ricorrente: Asse AhR-IL-22 come ponte plausibile tra antifungal mucosal defense e omeostasi intestinale.
6. NCGS??

# Prospettive: verso una post-biotica di precisione

## Stratificazione

Non “celiachia” in blocco, ma cluster: disbiosi persistente, basso SCFA, basso tono AhR, candidosi, sintomi IBS-like.

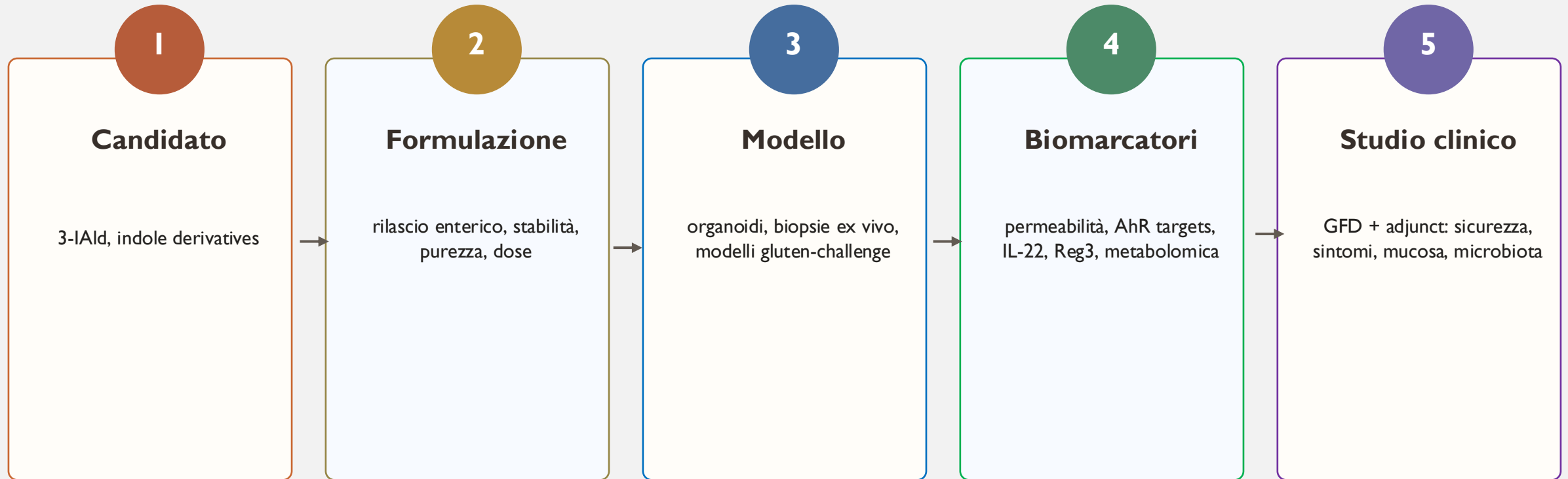
## Combinazioni

GFD + post-biotico; GFD + enzimi del glutine;  
GFD + prebiotico mirato; IAIId/SCFA con rilascio locale.

## Personalizzazione

Metabolomica fecale/serica, transcriptomics mucosale, organoidi da paziente e microbiome function testing.

# Pipeline di sviluppo: dal candidato al proof-of-concept secondo un meccanismo misurabile eD endpoints mucosale verificabili



# Endpoints: biomarcatori coerenti con il meccanismo

|                   |                                                                             |
|-------------------|-----------------------------------------------------------------------------|
| <b>Barriera</b>   | lattulosio/mannitolo, zonulina con cautela, claudine/occludina, istologia   |
| <b>Immunità</b>   | IEL, IFN- $\gamma$ , IL-15, IL-17/Treg, IL-22, Reg3, Cyp1a1                 |
| <b>Microbiota</b> | taxa + funzioni: glutenases, SCFA, indoli, <i>Candida</i> load              |
| <b>Clinica</b>    | dolore/gonfiore, qualità di vita, sierologia, Marsh se indicato             |
| <b>Sicurezza</b>  | assenza di glutine contaminante, immunogenicità, interazioni, tollerabilità |

# Network Pharmacology: the next paradigm in drug discovery

The holistic picture of multiple metabolites engaging with multiple targets, i.e., diverse metabolites interacting with a shared target and/or a single metabolite binding to diverse targets, represents a unique feature of these signal transduction systems that demands for a

**multitarget-directed approach**

This polypharmacology is the strength and the challenge of postbiotics:

- Few targets are missed
- But mechanistic dissection is harder

# Limitations and Open Questions

- Lack of standardization across postbiotic formulations.
- Need for mechanistic biomarkers and multi-omics integration.
- Optimal dosing, duration and patient selection remain unclear.
- Regulatory classification is still evolving.

Thanks



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# I POSTBIOTICI

