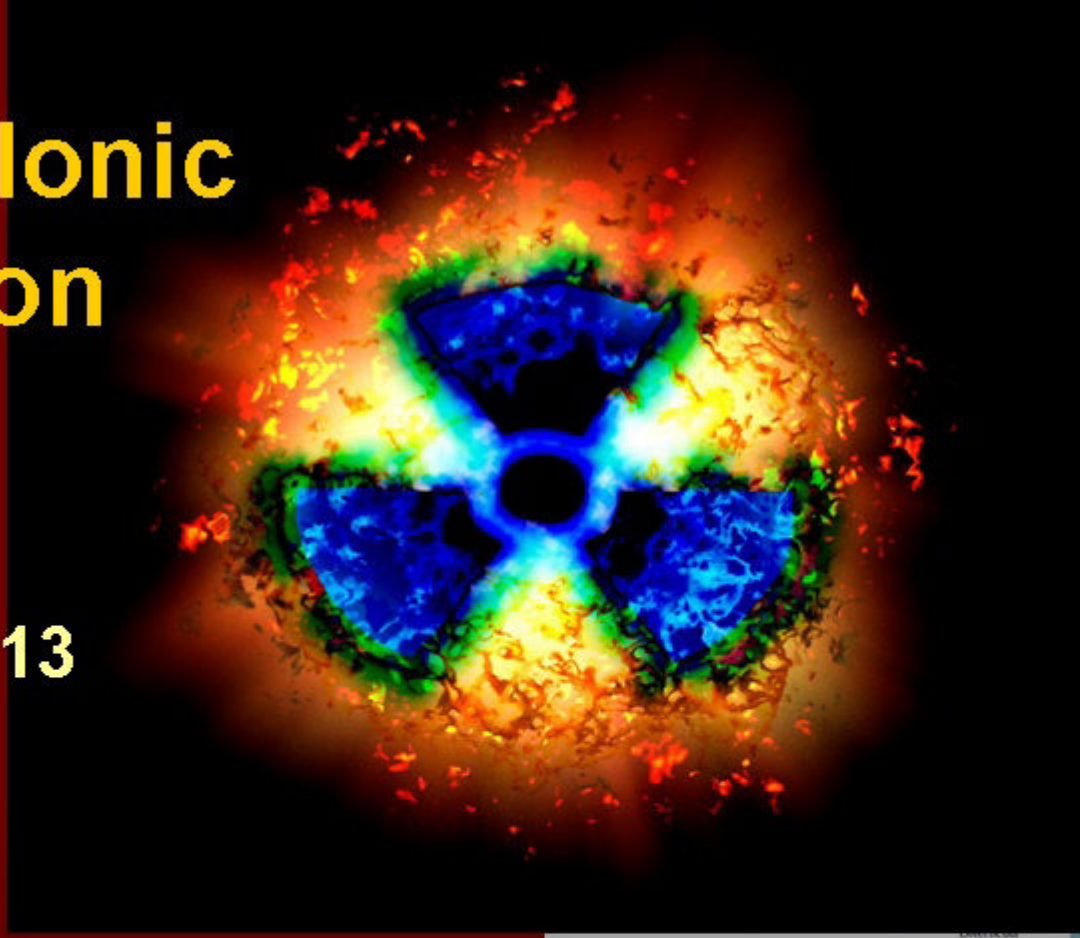
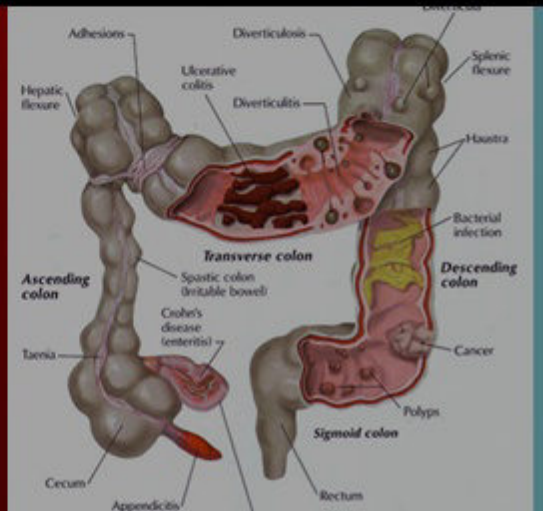
Hazards of colonic Biofermentation



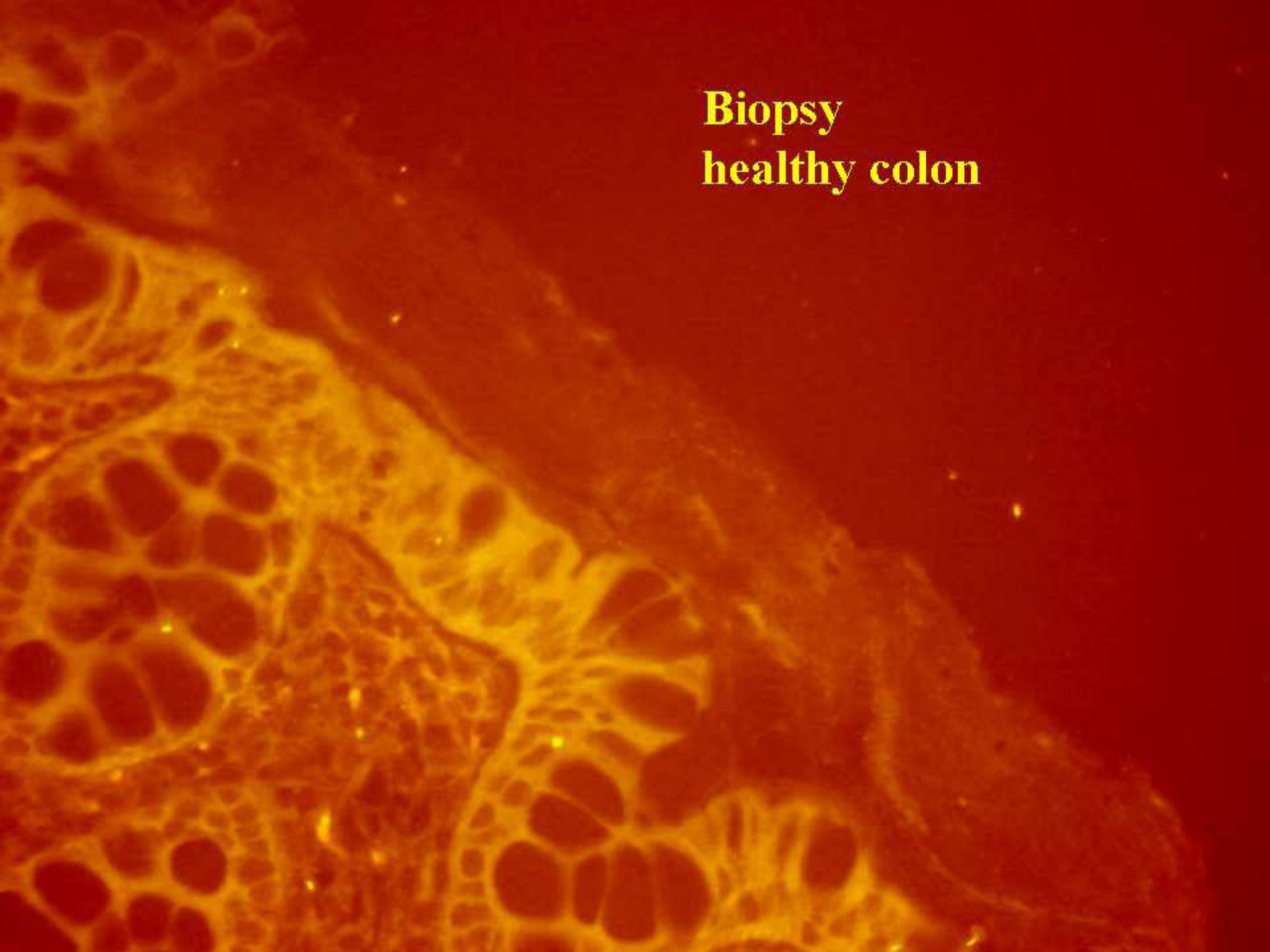
all bacteria 10^{13}

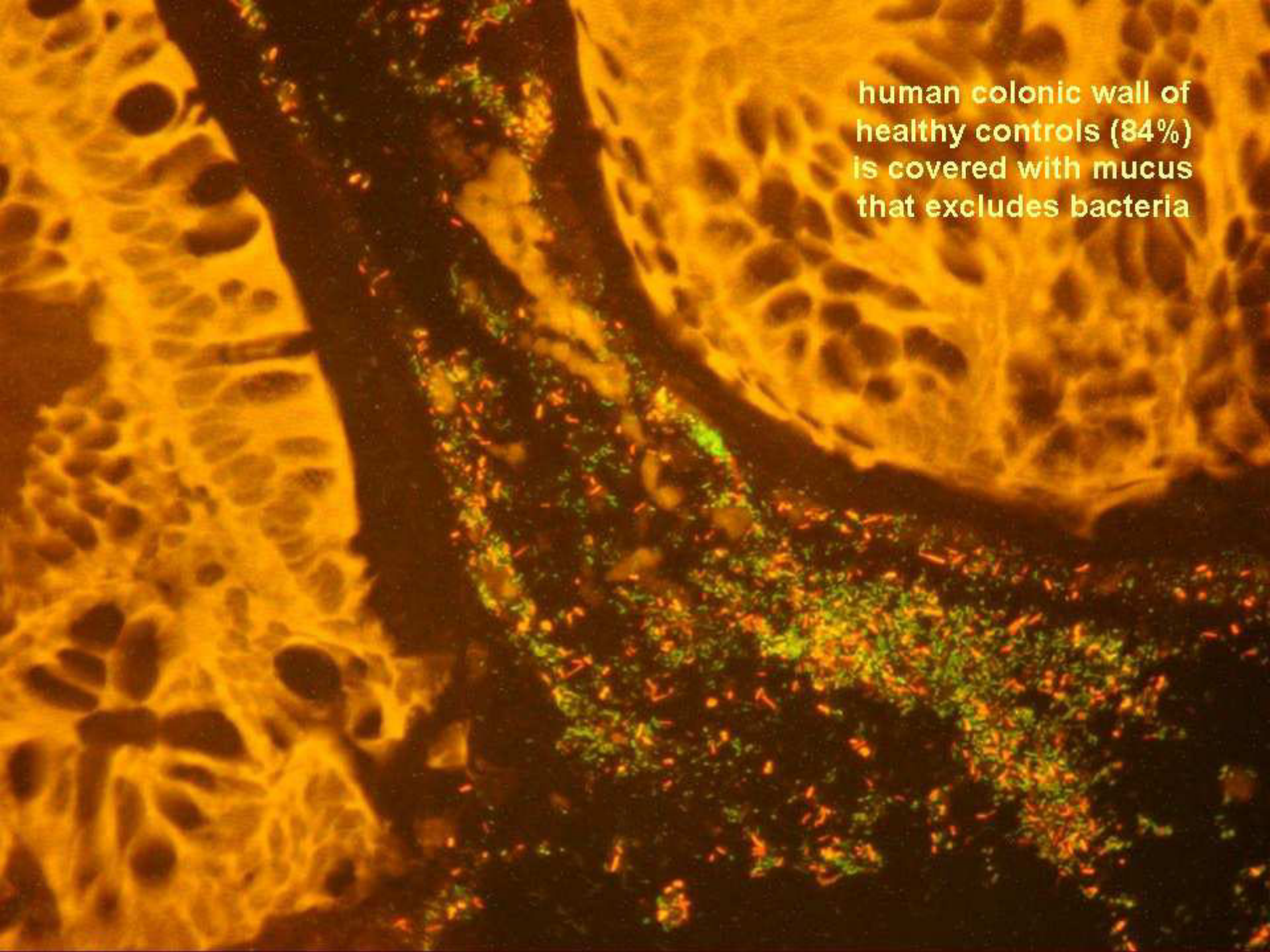
- $>10^{10}$
- Clostridium perfringens (gas gangrene)
- Enterococci (Endocarditis)
- Bacteroides (Abscess)
- E.coli (Sepsis)
  - 1/5 has Clostridium botulinum !!!

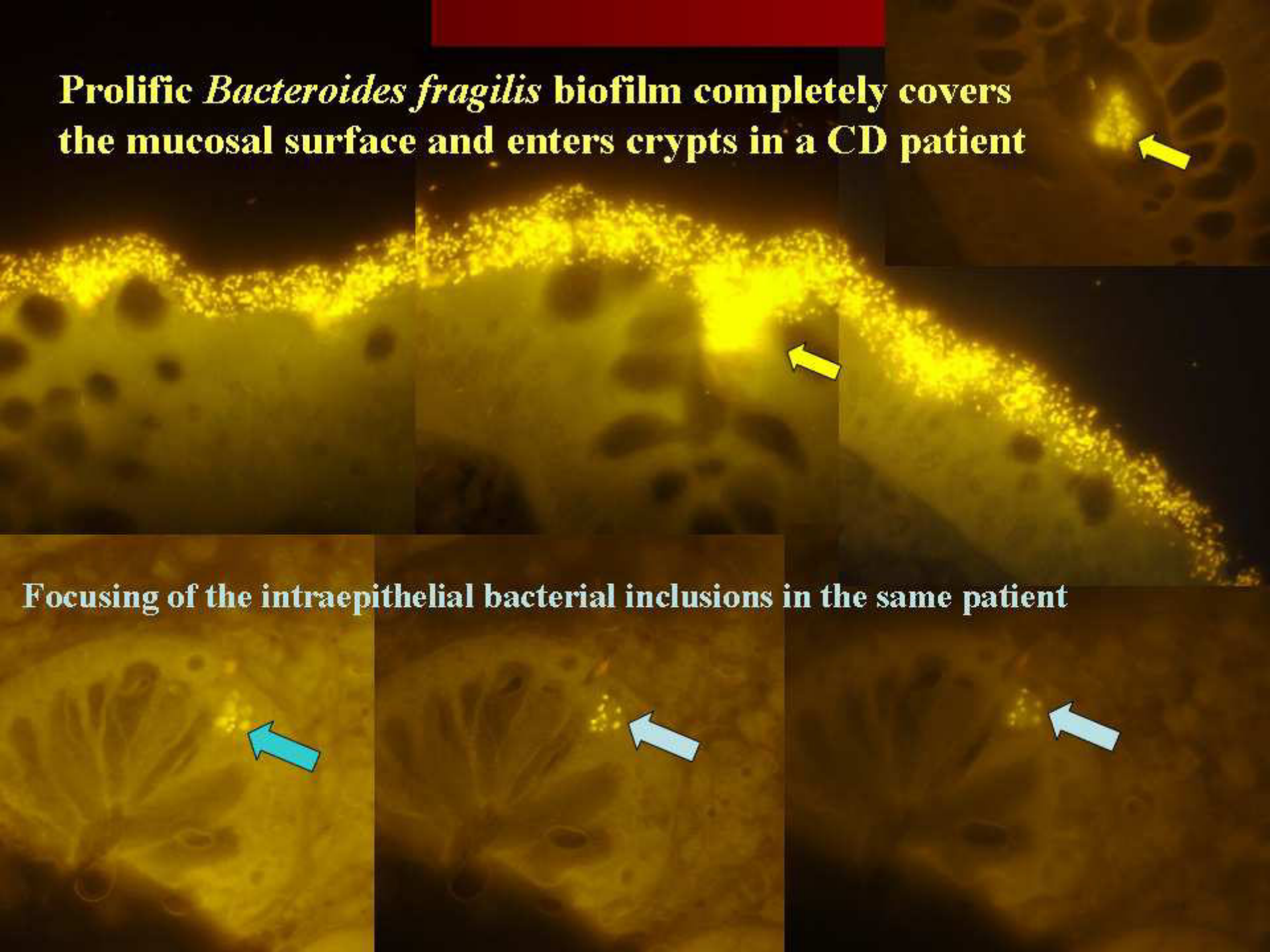


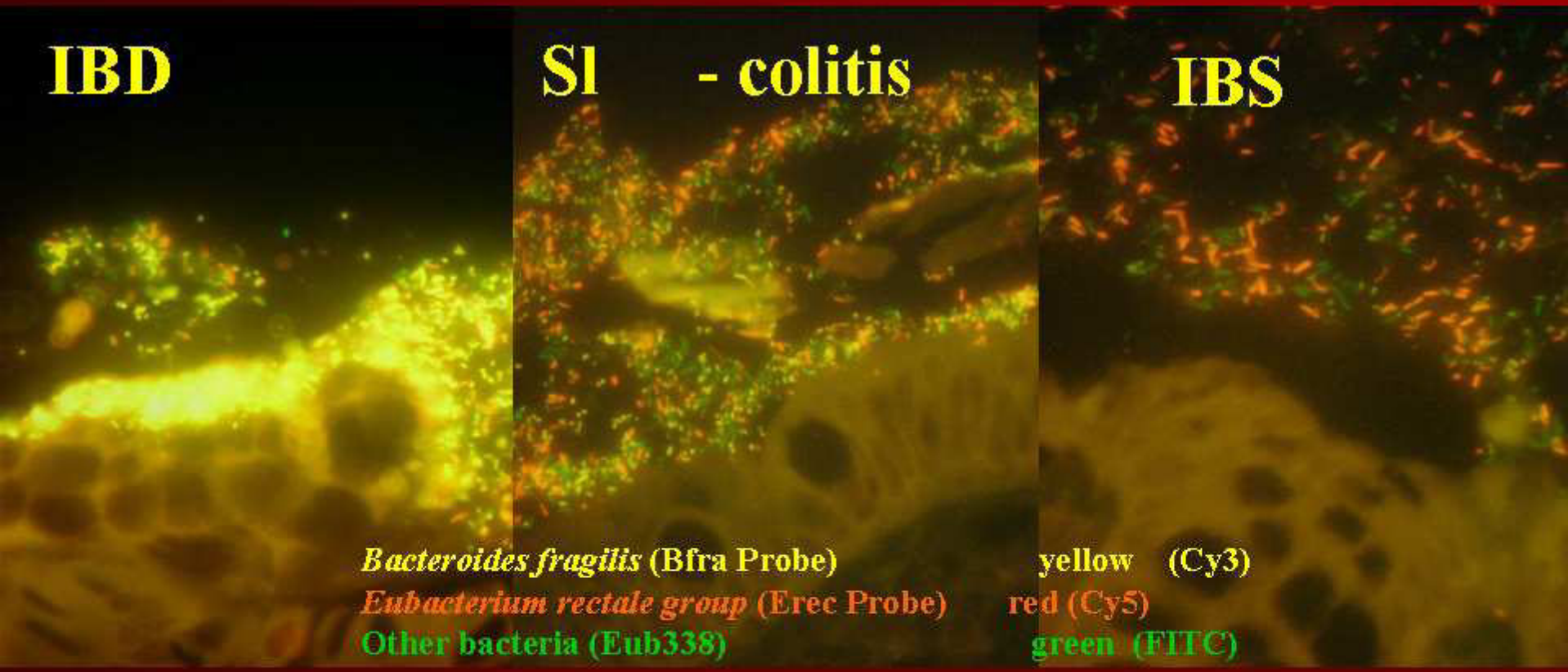
Human made biorectors

Maximal concentrations achievable 10^{10}


Biopsy
healthy colon


human colonic wall of
healthy controls (84%)
is covered with mucus
that excludes bacteria

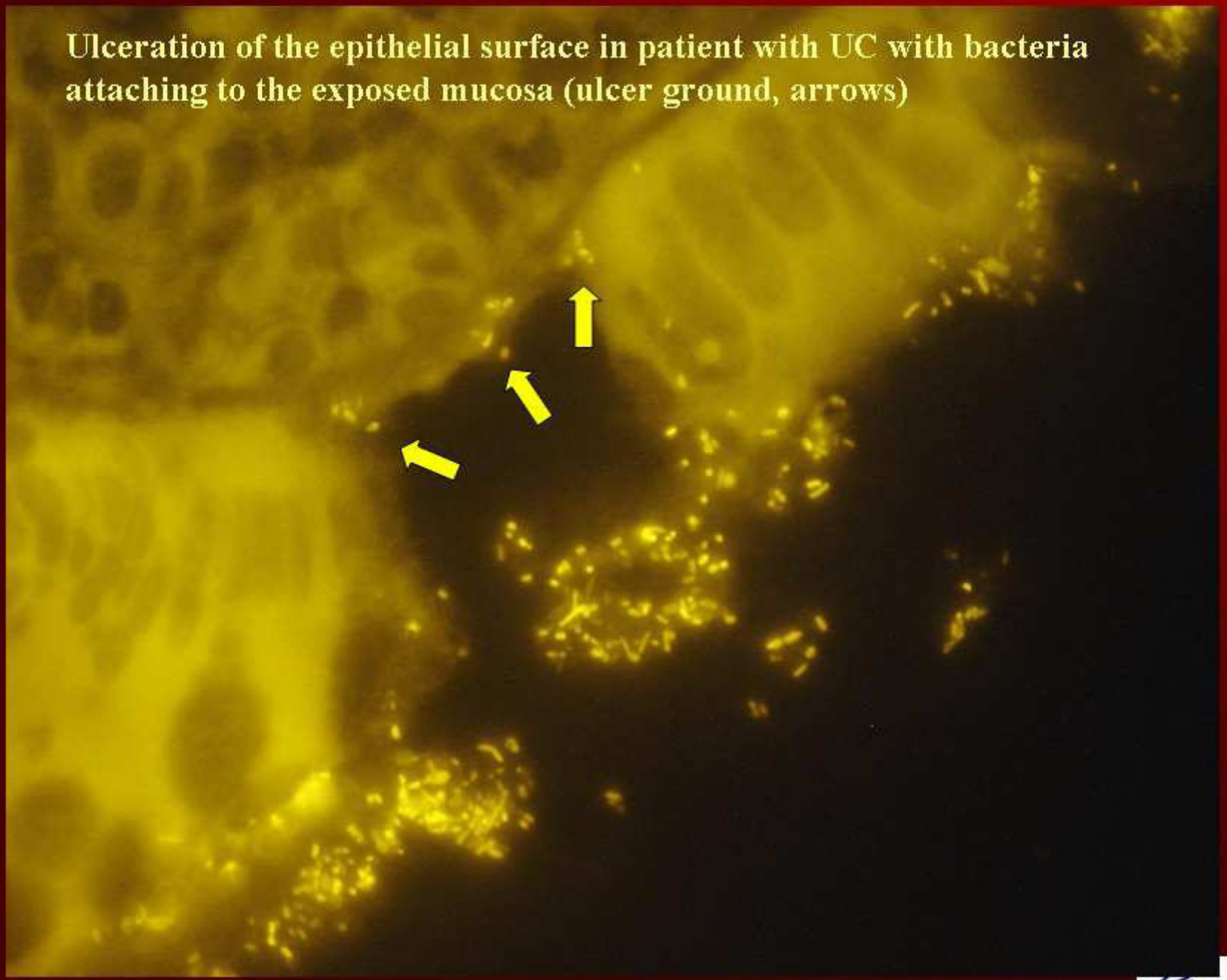

Prolific *Bacteroides fragilis* biofilm completely covers the mucosal surface and enters crypts in a CD patient
Focusing of the intraepithelial bacterial inclusions in the same patient

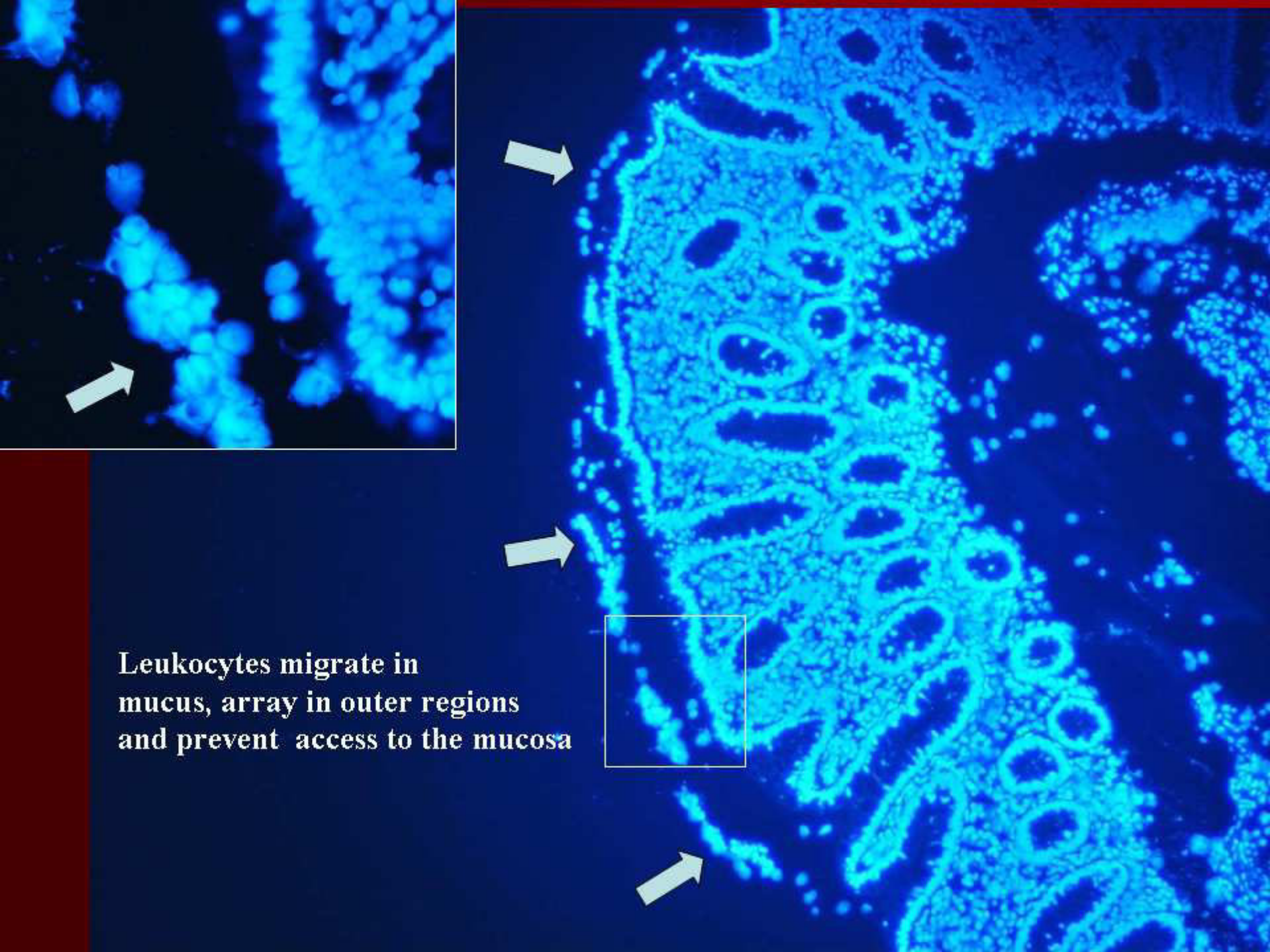


Percent of patients with 10^9 bacteria/ml

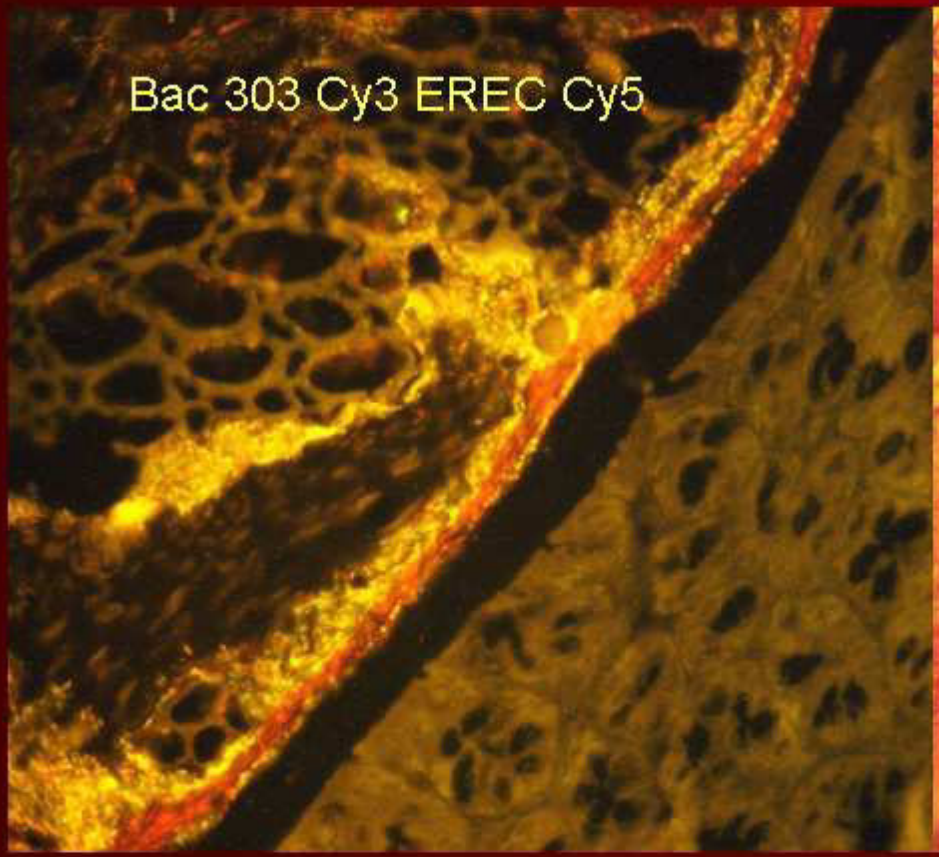
Percent of bacteria within biofilm

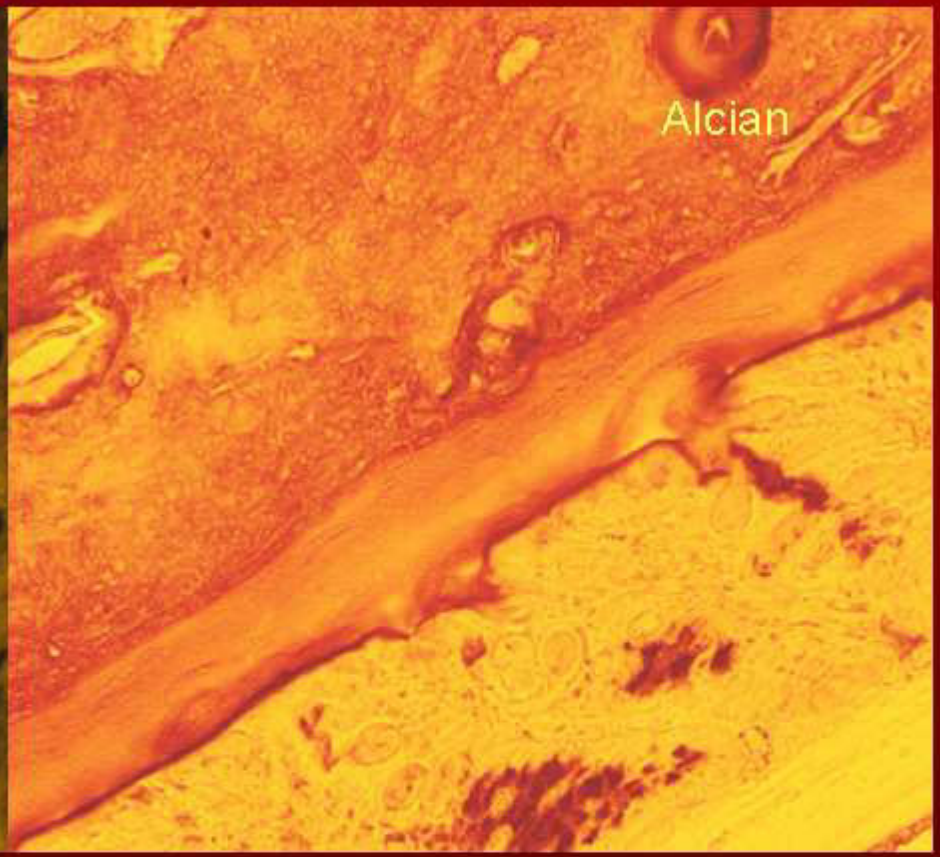
	CD 98%	UC 94%	SIc 78%	IBS 38%	Contr. 16%
Bfra	60%	30%	31%	14%	16%
Erec	10%	5%	18%	48%	32%


Ulceration of the epithelial surface in patient with UC with bacteria attaching to the exposed mucosa (ulcer ground, arrows)

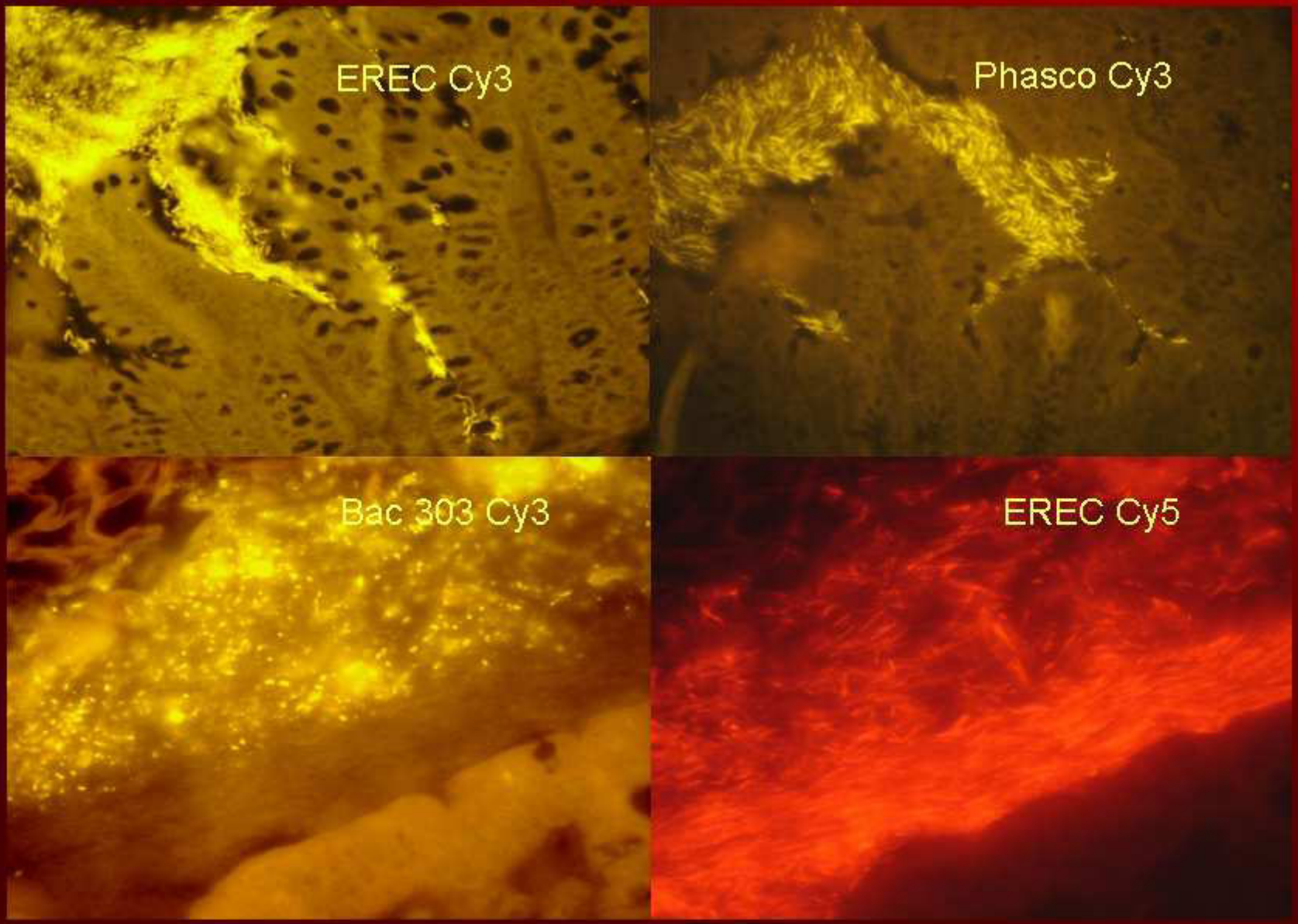

Leukocytes migrate in
mucus, array in outer regions
and prevent access to the mucosa

The number of bacteria in small intestine
of a healthy wild type mouse
is low



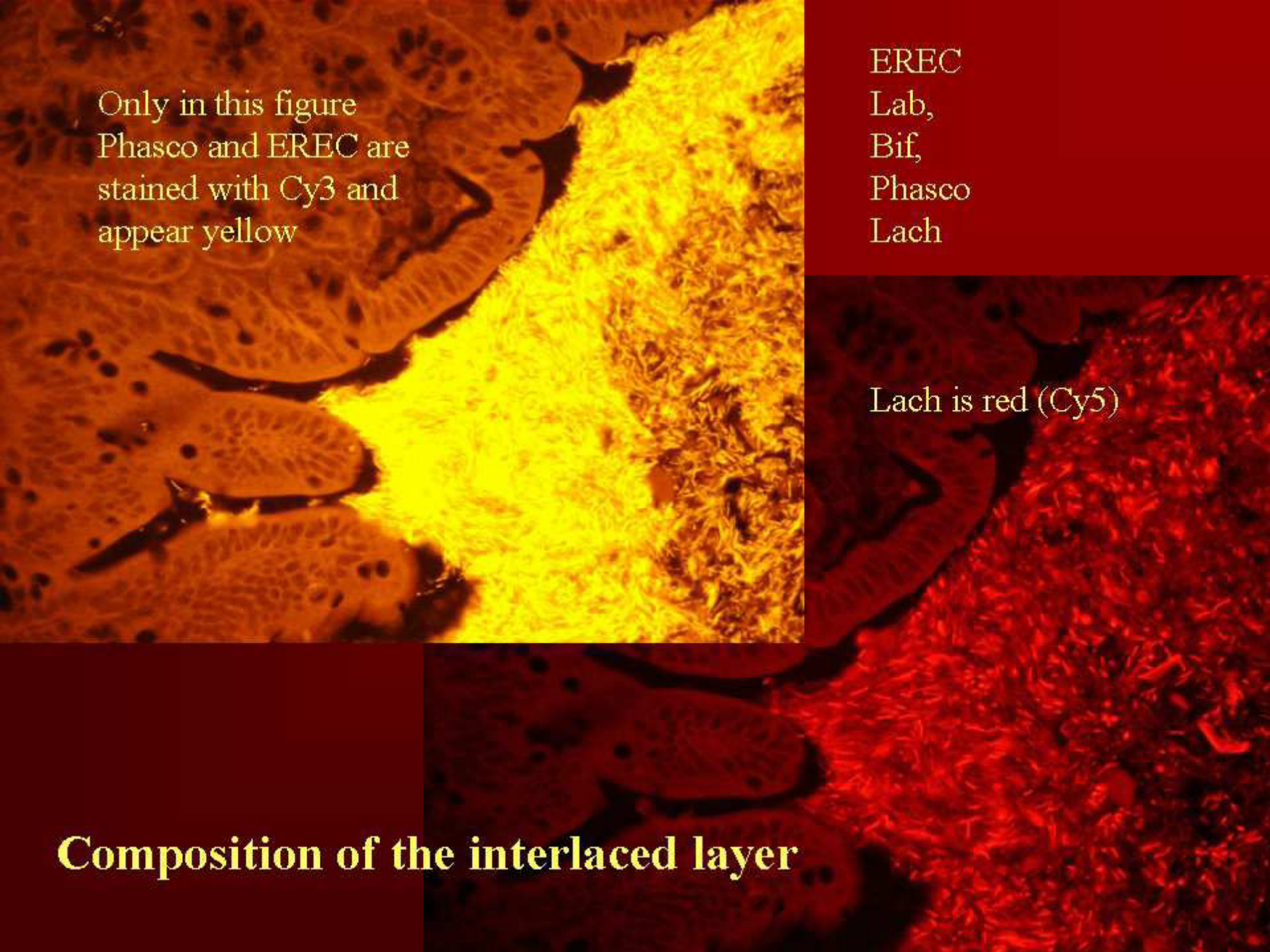


The mucus completely separates mucosa from feces in distal colon of mice similar to the situation in man



The separation of bacteria in the proximal colon of mice is selective, EREC enters crypts, *Bacteroides has no contact with colonic wall*

Short rods of *Bacteroides, Enterobacteriaceae, Clostridium difficile, Veillonella* groups have no contact with the colonic wall

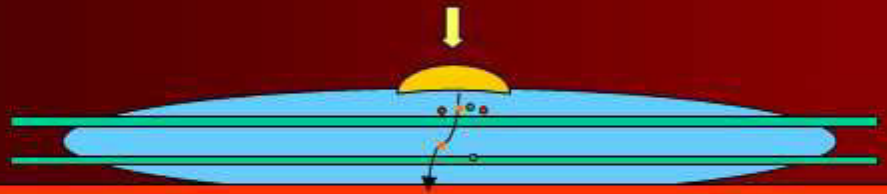


Composition of the interlaced layer

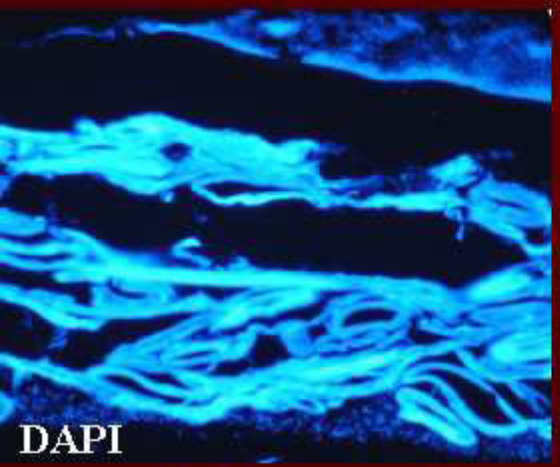
Mucus simulation in vitro

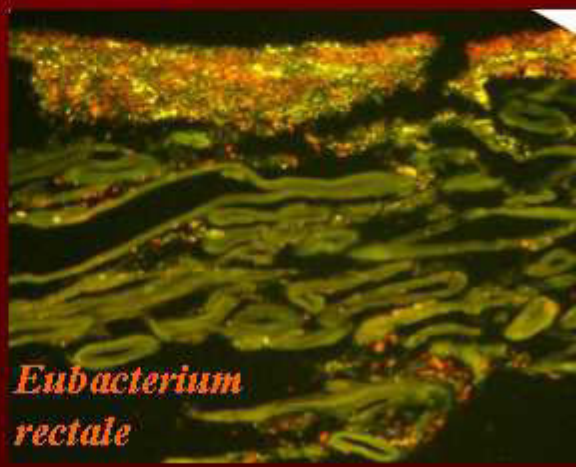
Native mix of fecal bacteria

Two layers of cellulose covered with a LB-agarose gel of variable viscosity

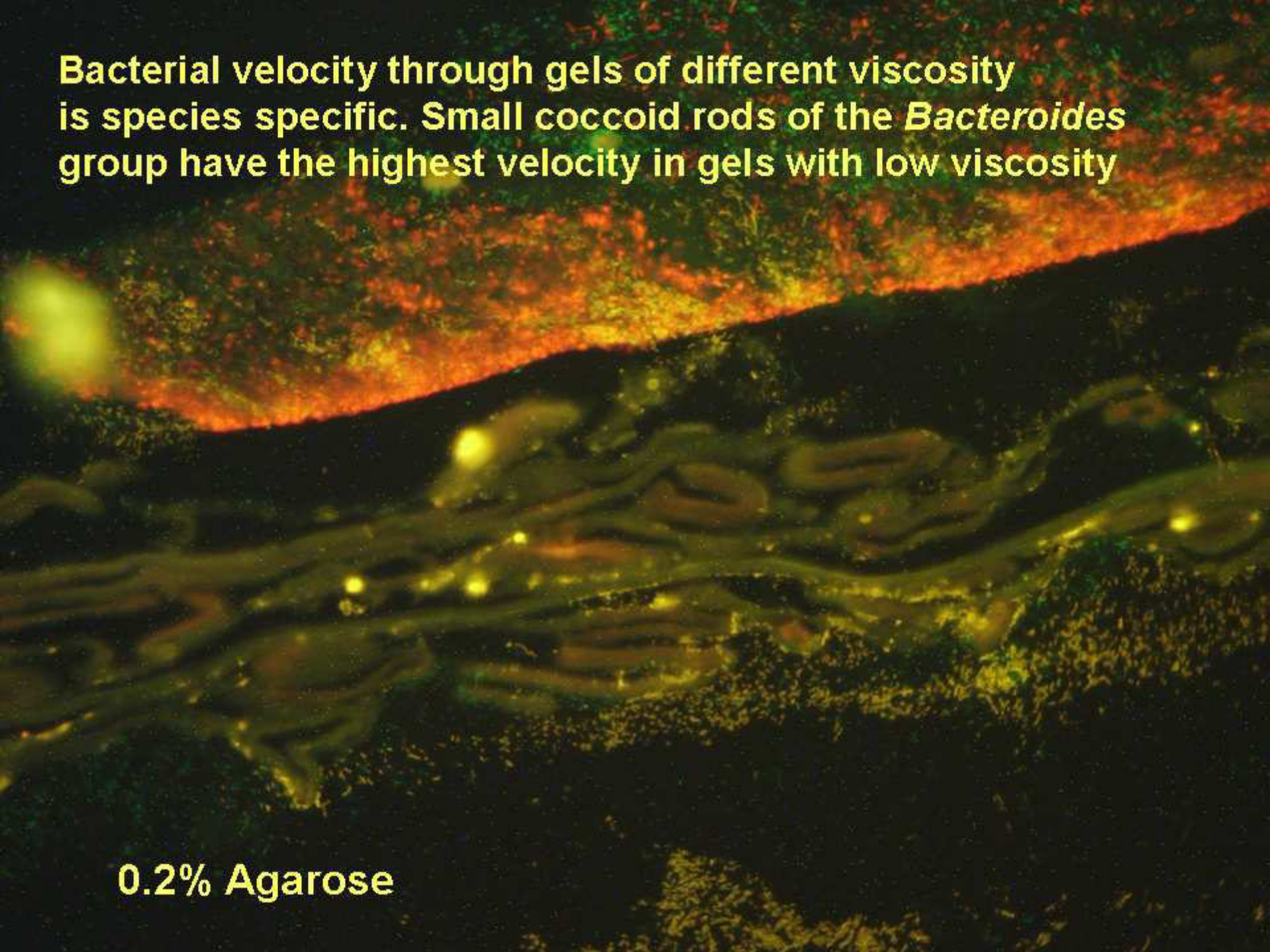


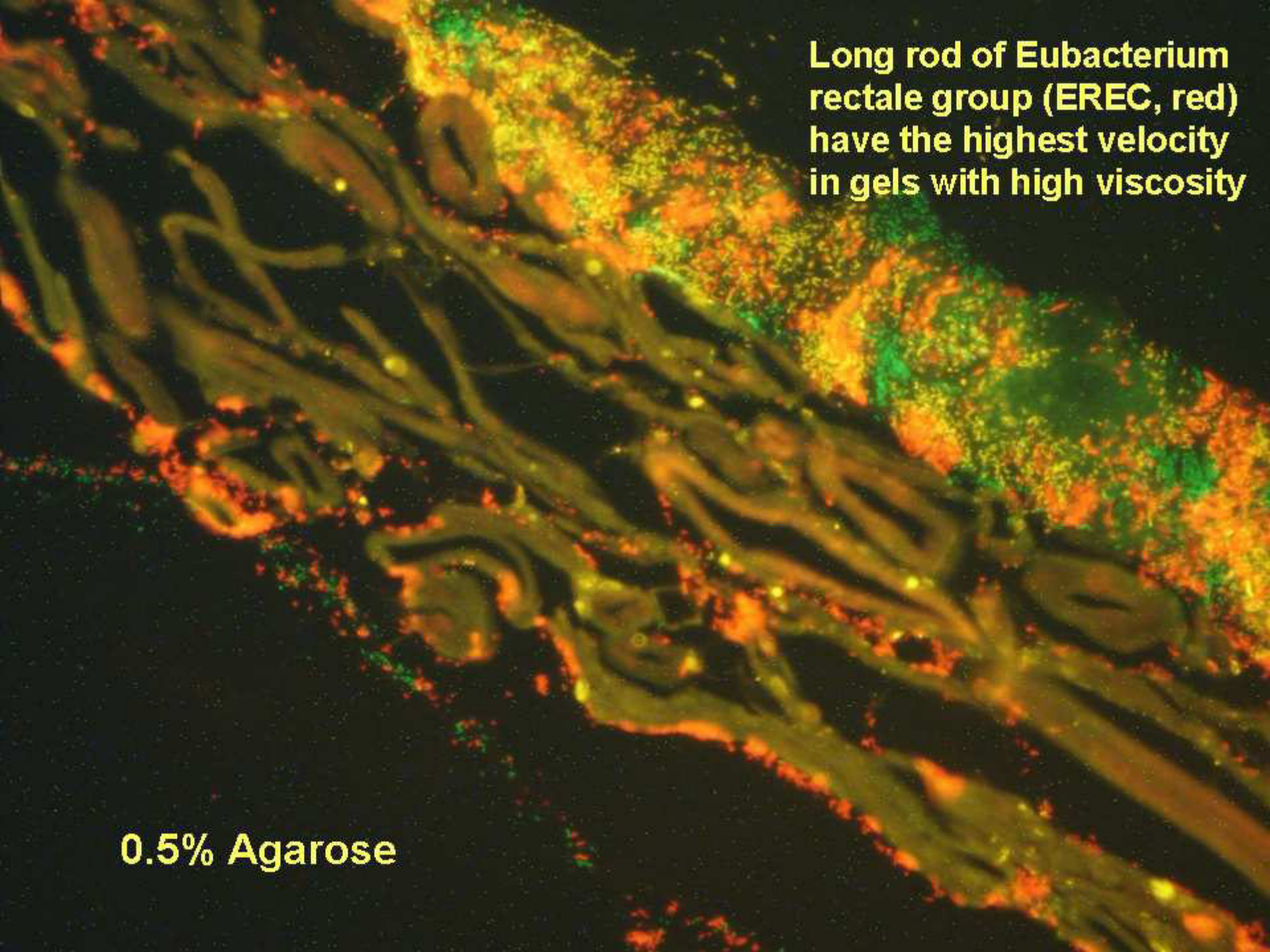
Blood agar plate





Examples of mobility


Bacterial velocity through gels of different viscosity
is species specific. Small coccoid rods of the *Bacteroides*
group have the highest velocity in gels with low viscosity
0.2% Agarose


Long rod of Eubacterium rectale group (EREC, red) have the highest velocity in gels with high viscosity
0.5% Agarose

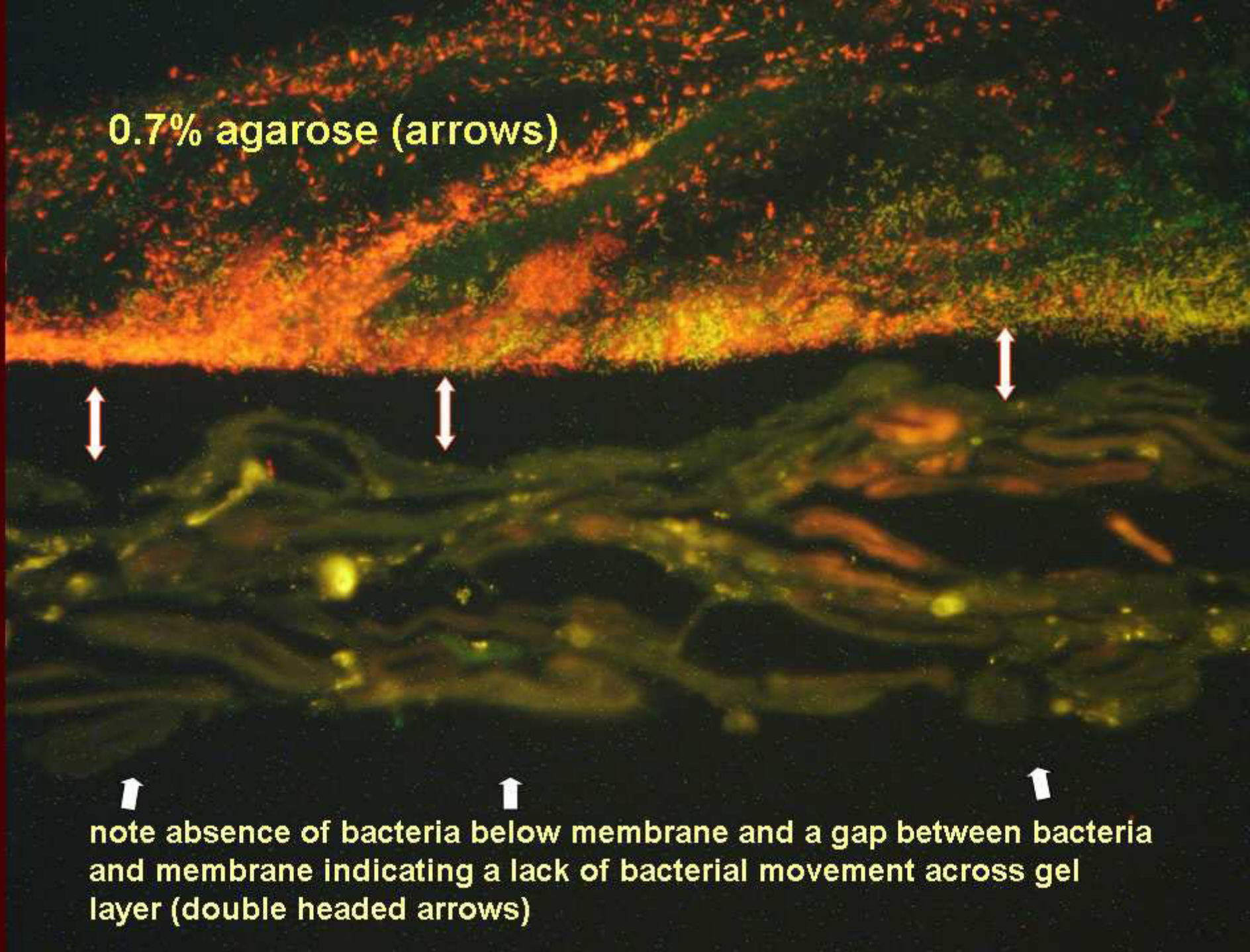
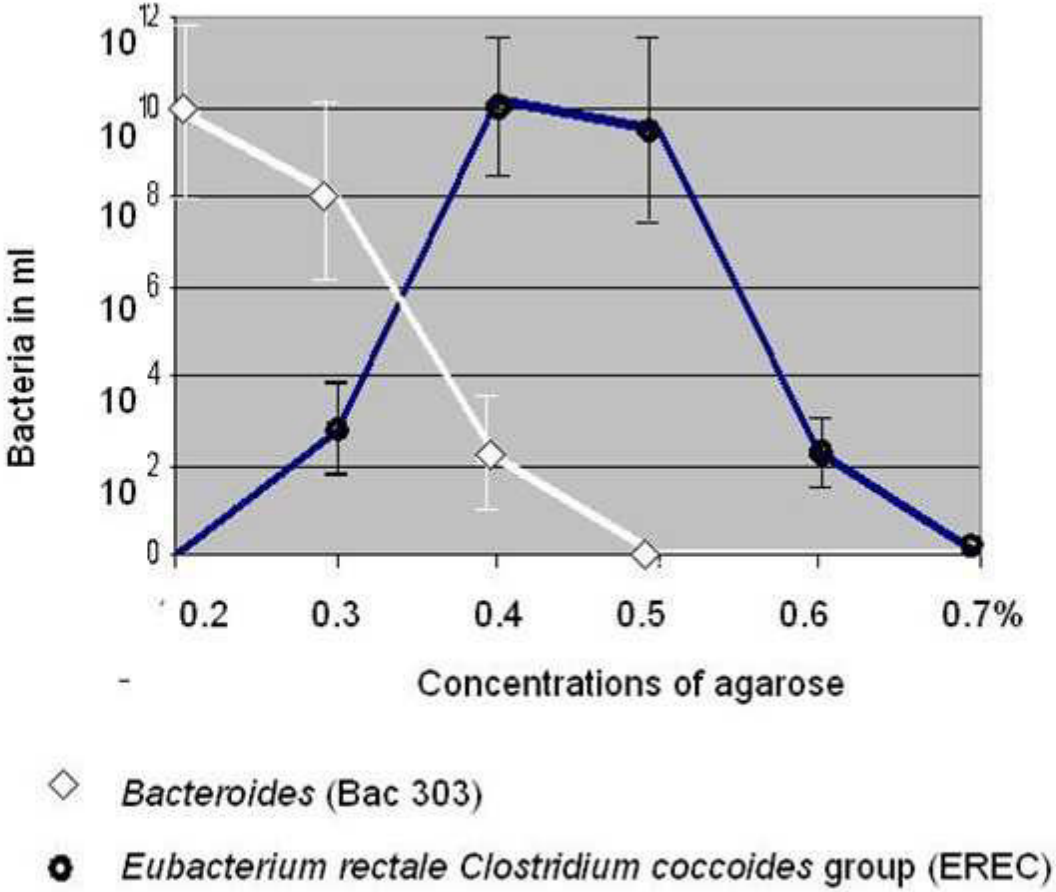
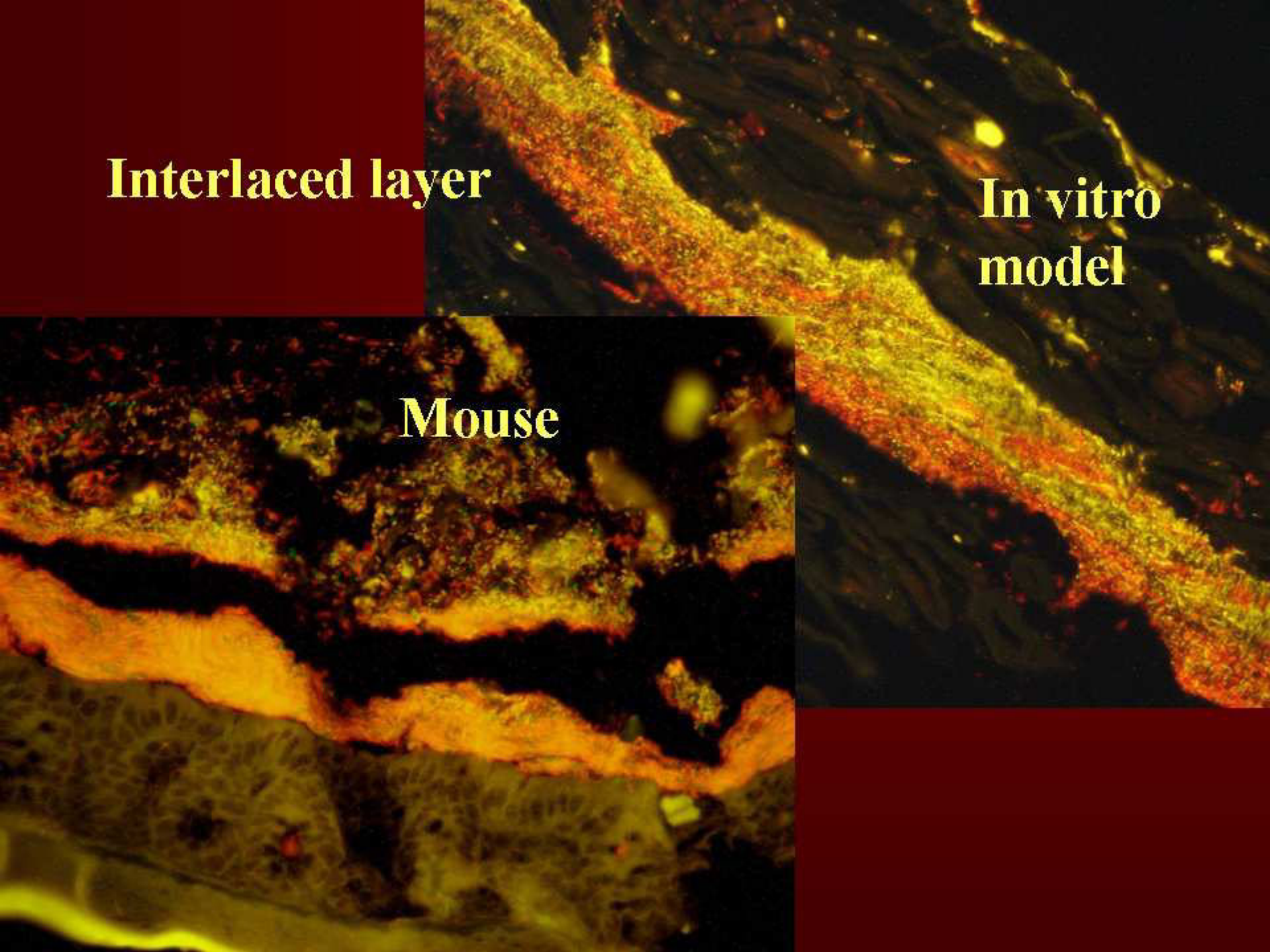
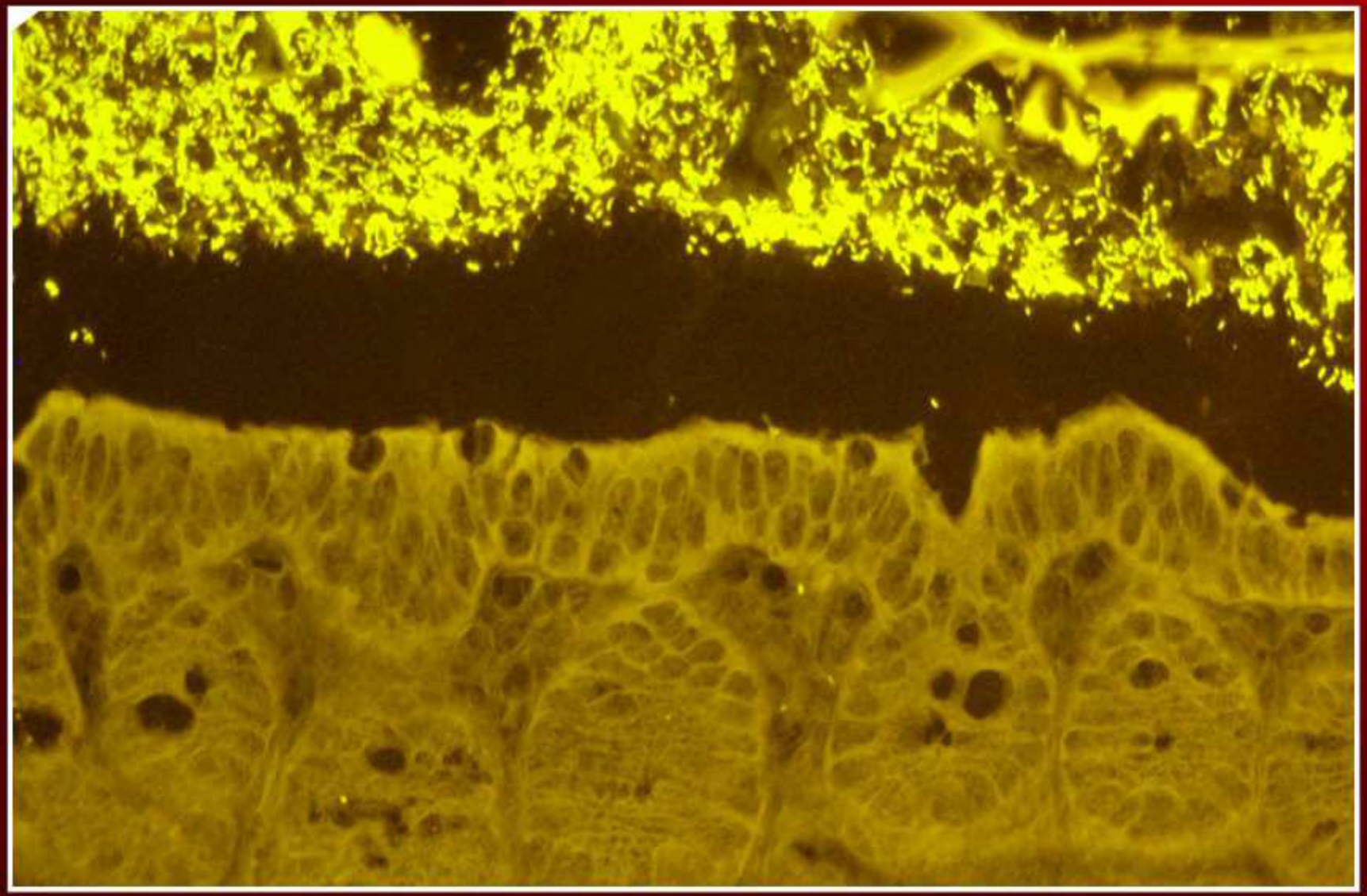

0.7% agarose (arrows)
note absence of bacteria below membrane and a gap between bacteria and membrane indicating a lack of bacterial movement across gel layer (double headed arrows)

Figure 2

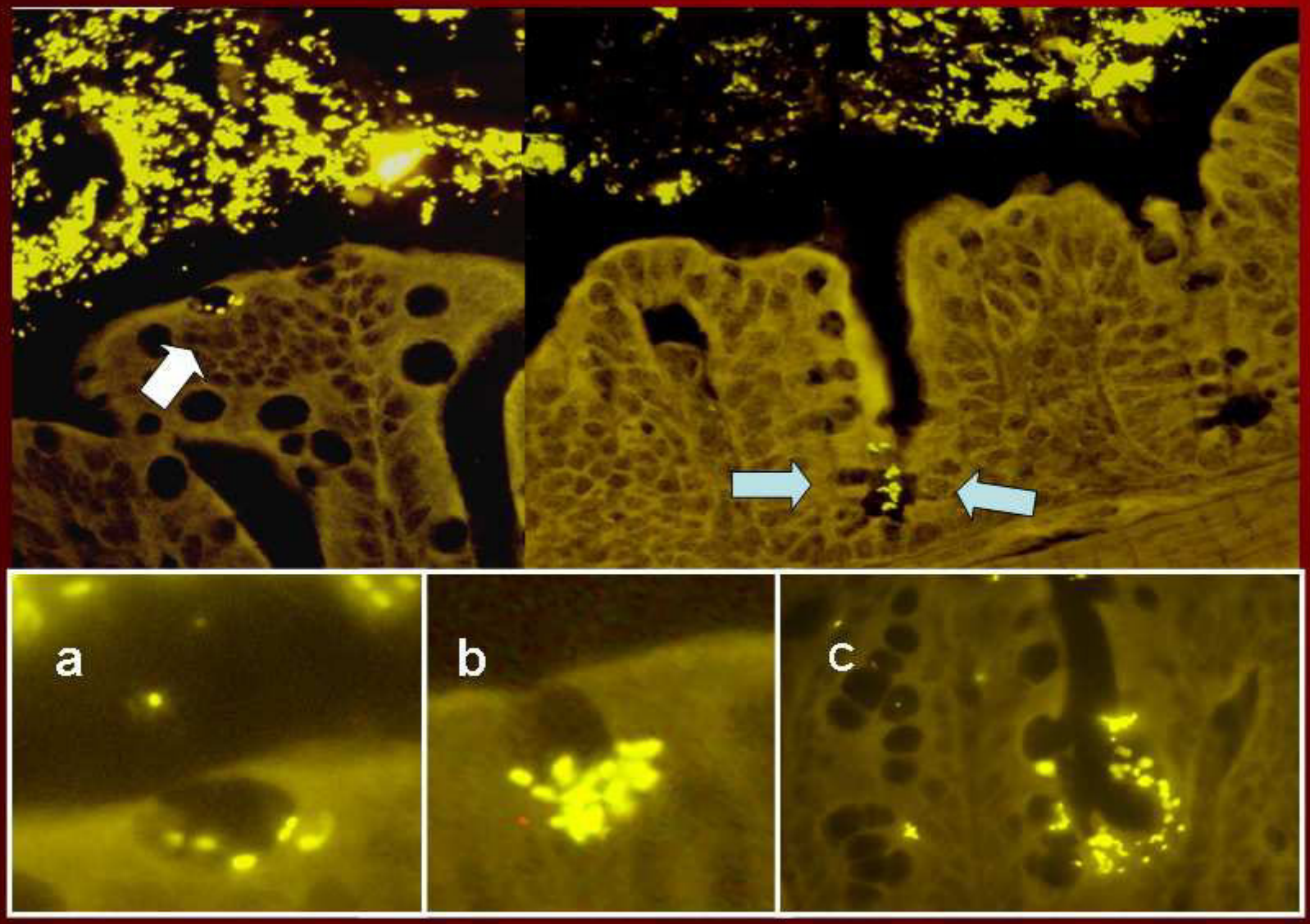


The viscosity-dependent changes in the concentrations
of bacteria moving across *LB-agarose* after 20 hours of anaerobic growth.

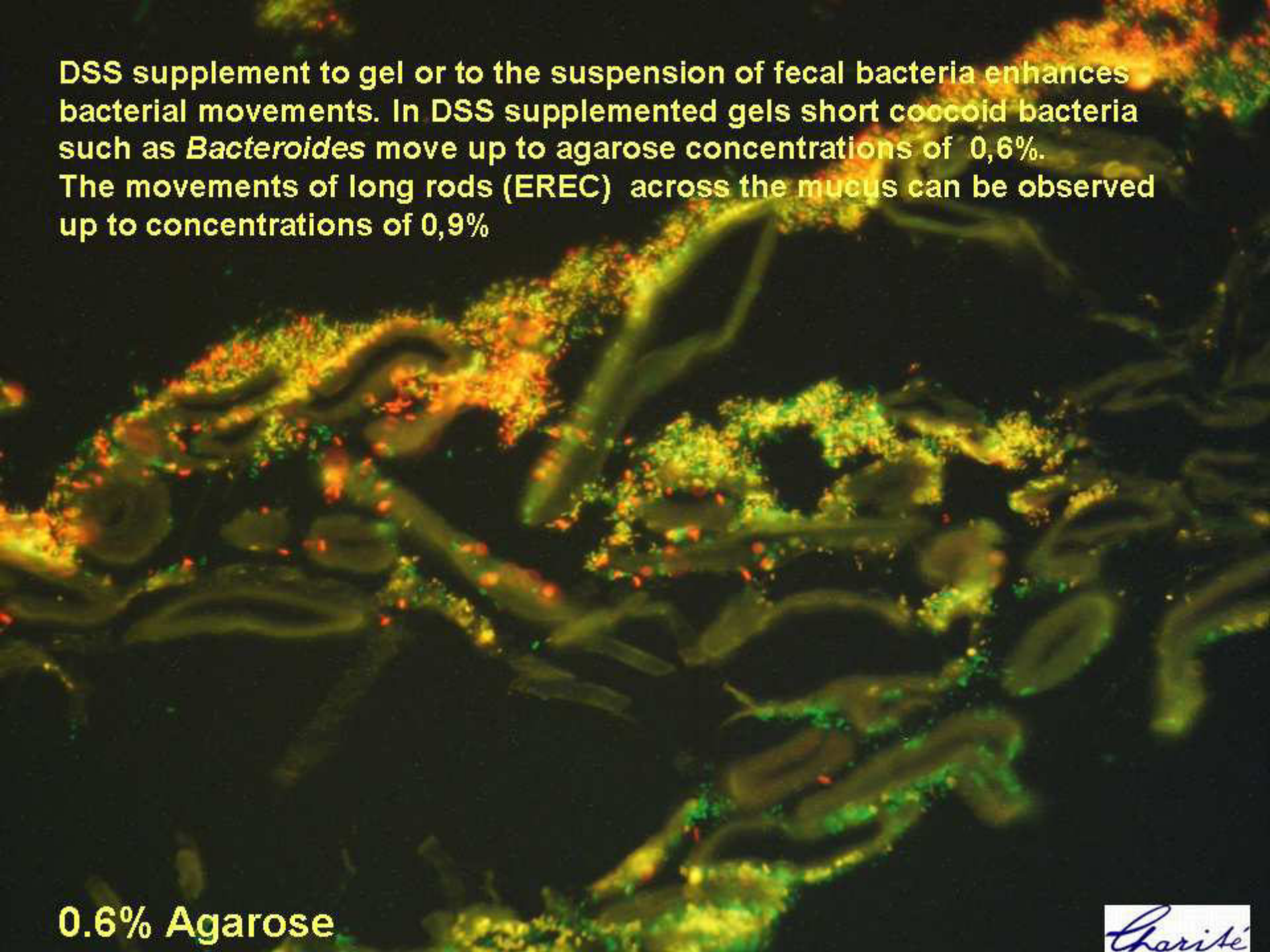

Interlaced layer
In vitro model
Mouse

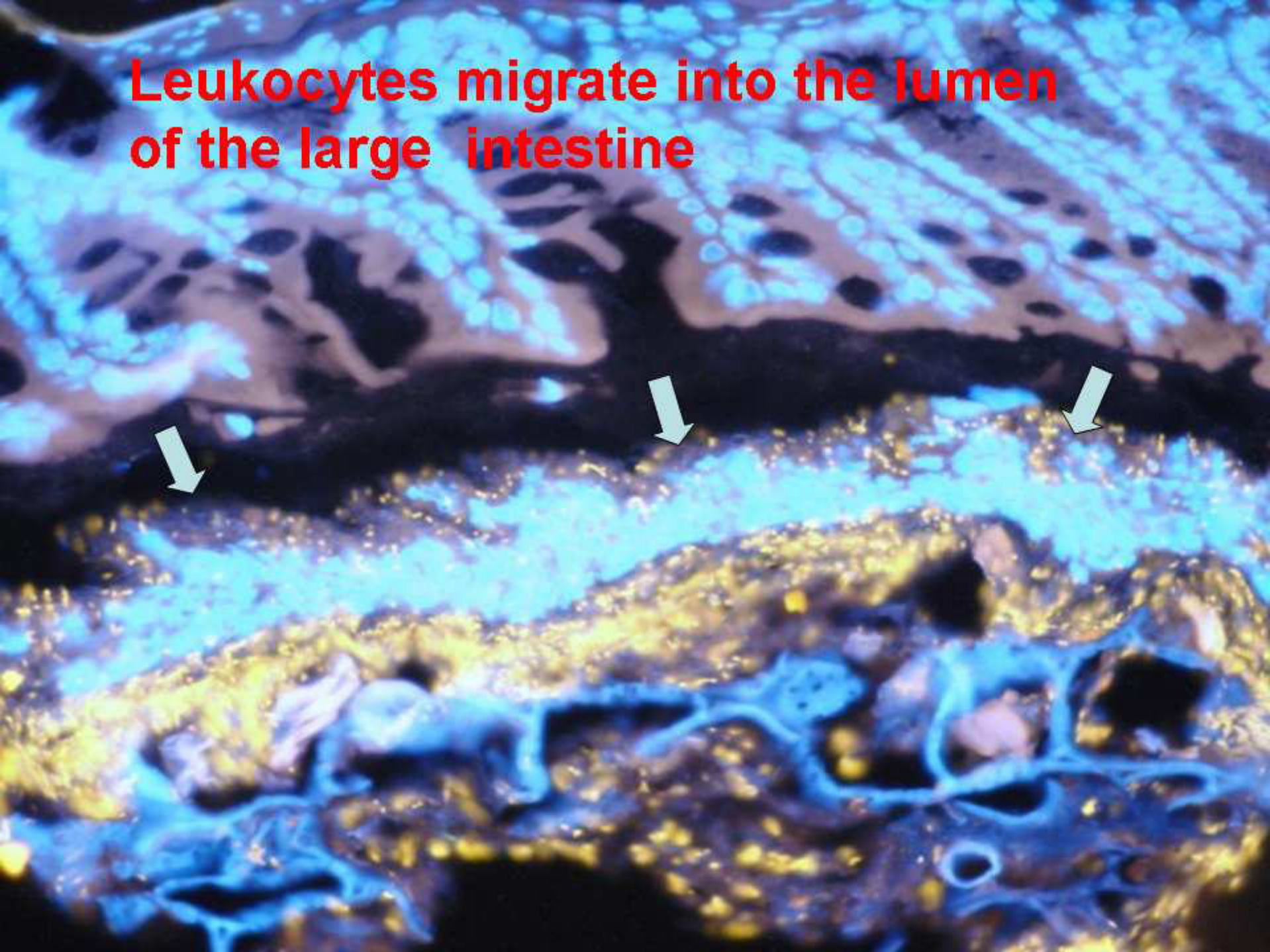


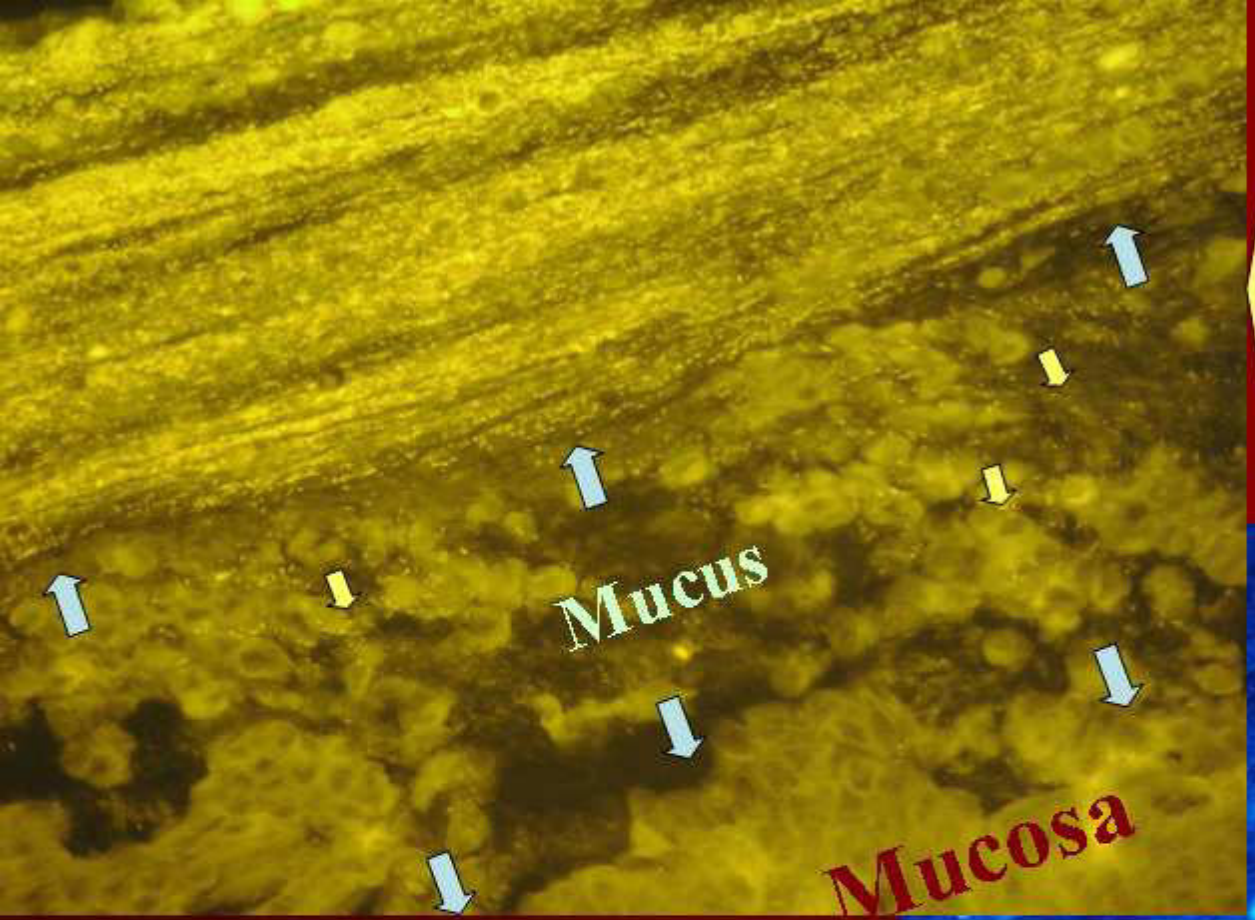
- Distal colon of mice mono-associated with *Enterobacter cloacae*



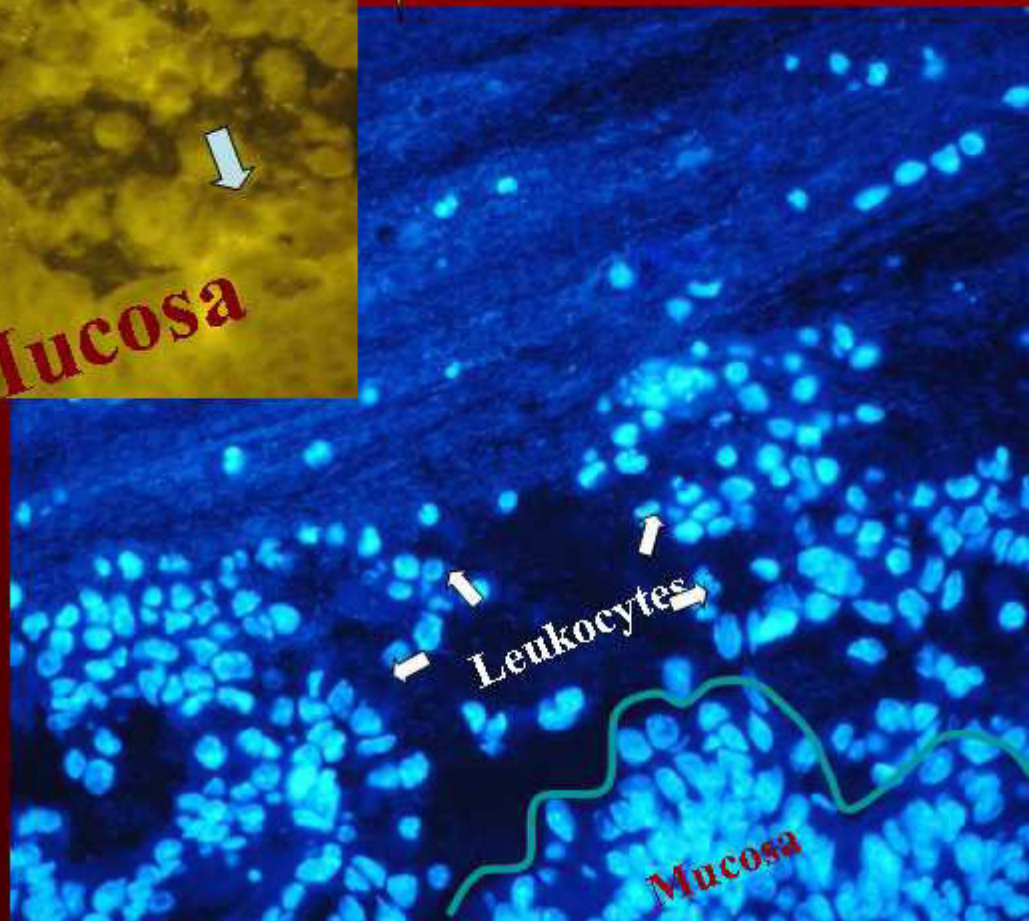
Proximal colon of mice mono-associated with *Enterobacter cloacae*


DSS supplement to gel or to the suspension of fecal bacteria enhances bacterial movements. In DSS supplemented gels short coccoid bacteria such as *Bacteroides* move up to agarose concentrations of 0,6%.
The movements of long rods (EREC) across the mucus can be observed up to concentrations of 0,9%
0.6% Agarose

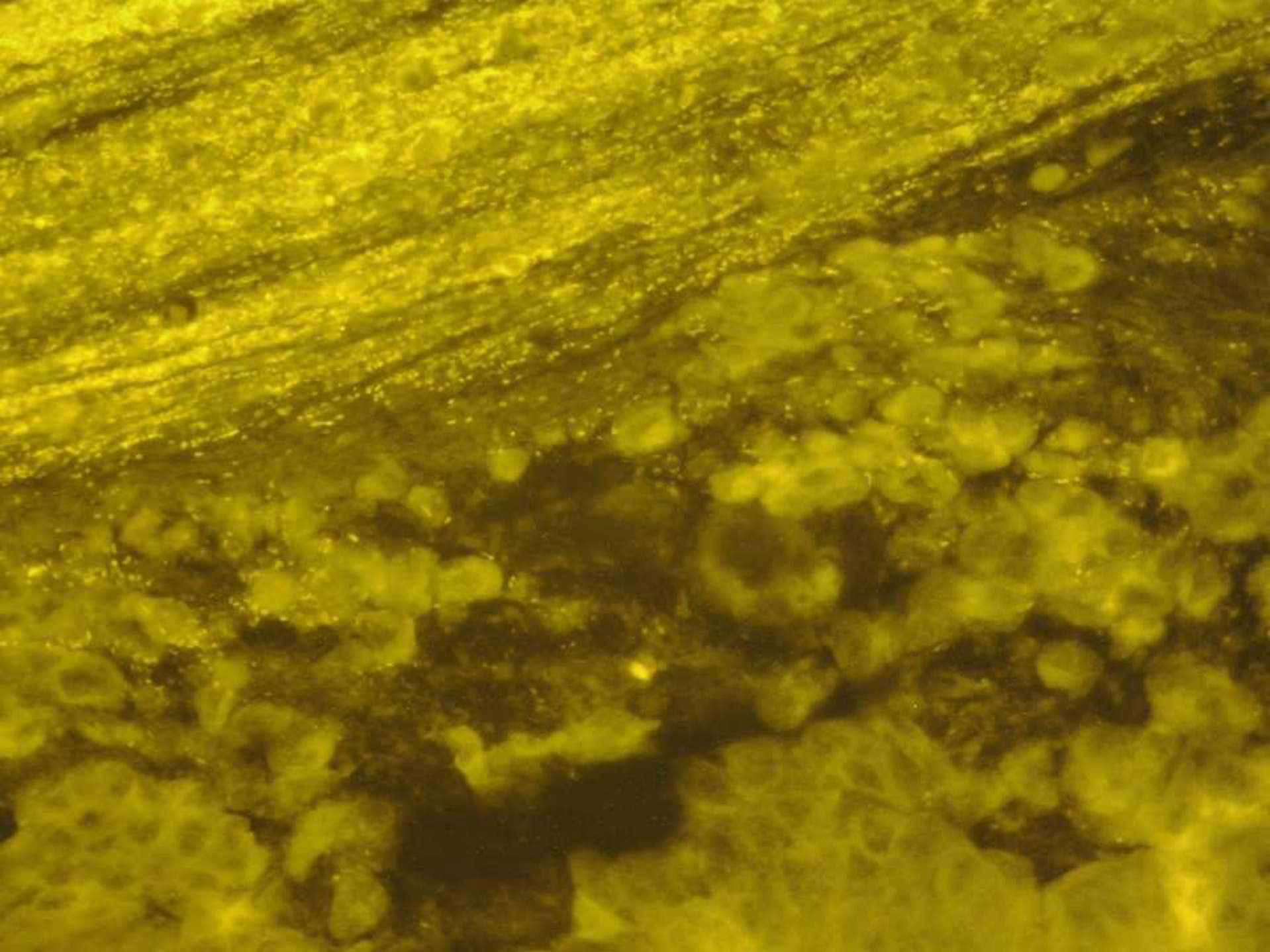

Leukocytes migrate into the lumen
of the large intestine



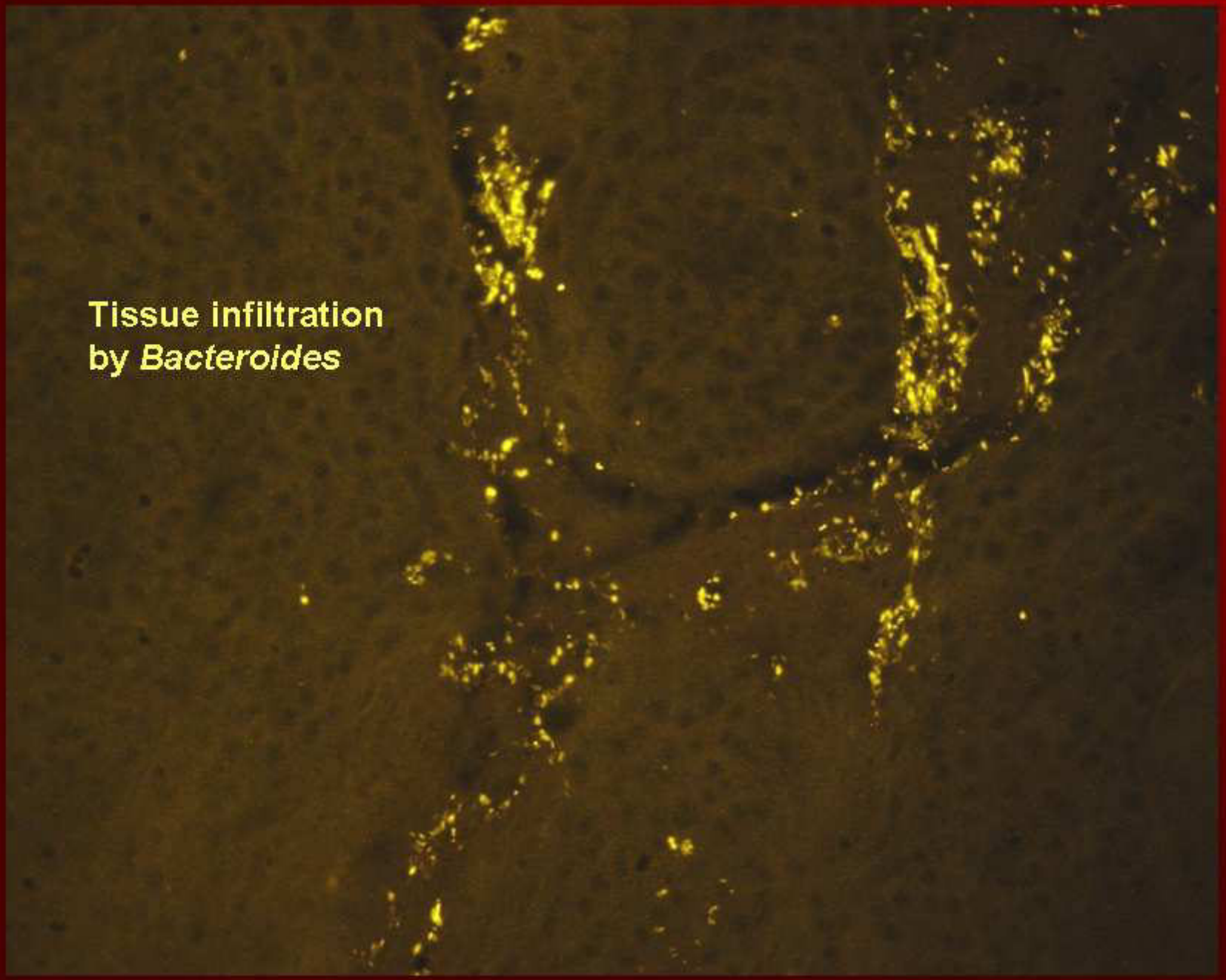
Bacteroides crosses mucus



The same microscopic field in DAPI shows leukocytes (large blue nuclei) migrating in mucus and hindering *Bacteroides* movement towards mucosa, normally only single leukocytes are present in mucus

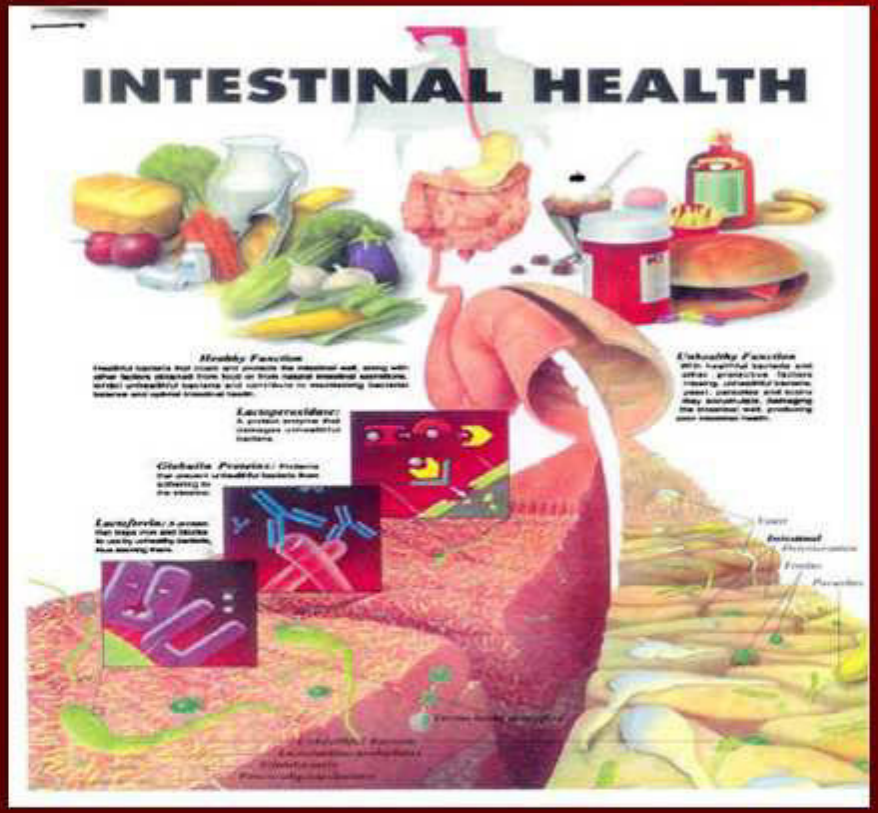



Bacteroides-adhesion to the colonic wall


Tissue infiltration
by *Bacteroides*

Tolerance

normal
Flora



Inflammatory Response

Enteral
Pathogens

E. coli

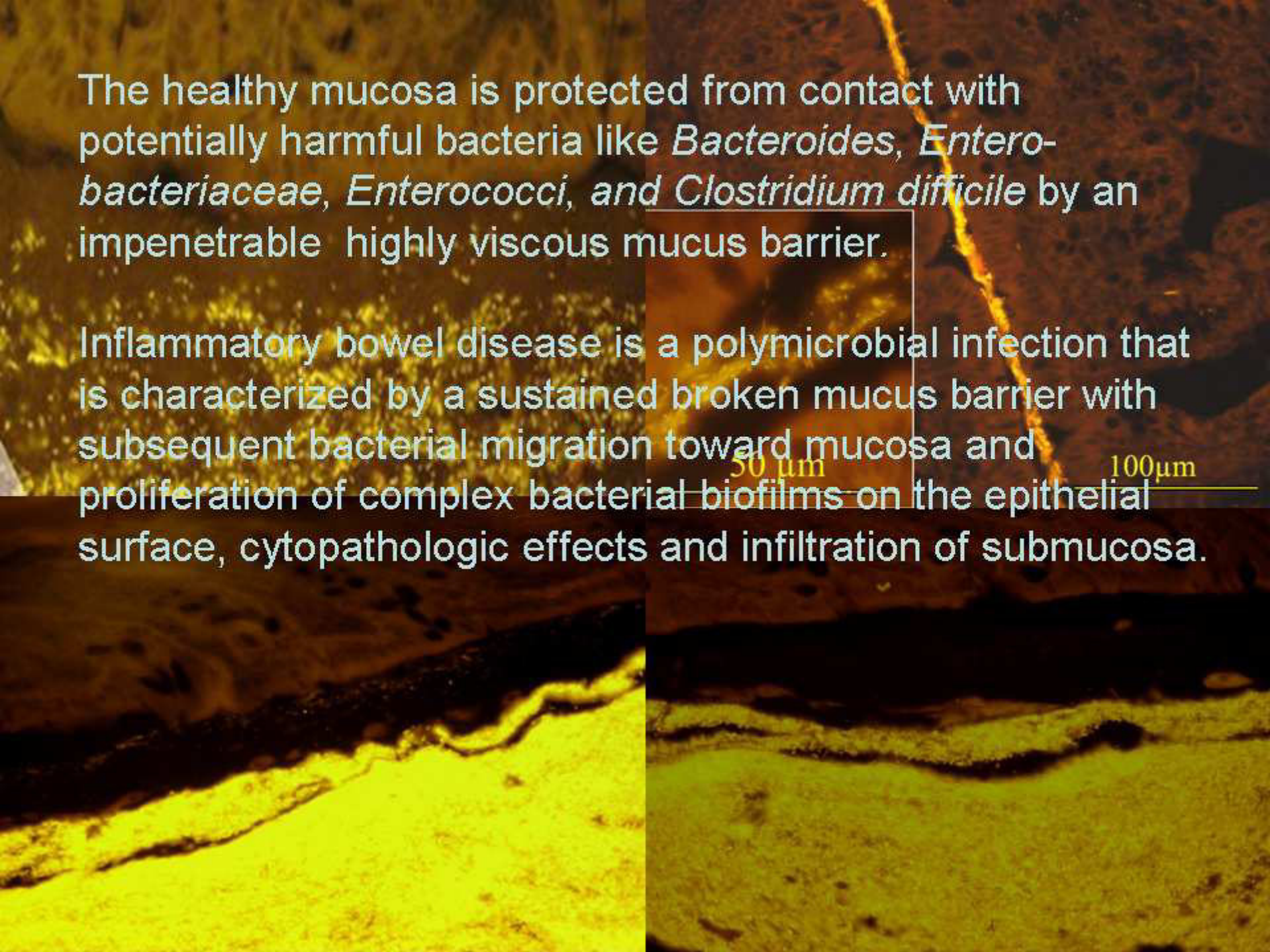
Bacteroides

Clostridium difficile

Enterococci

Salmonella

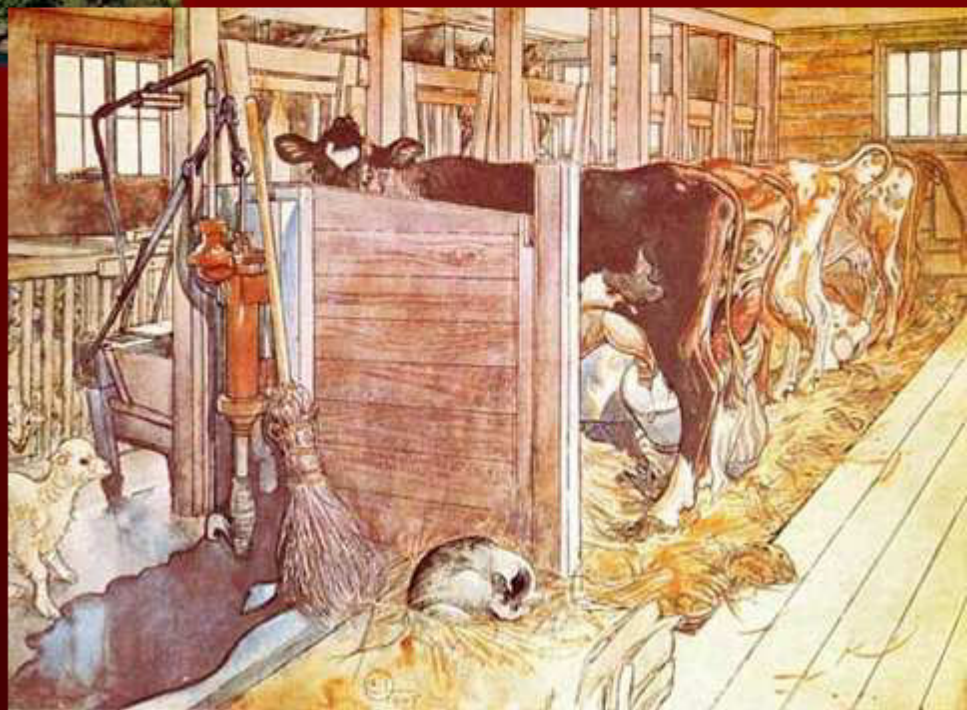
Shigella



The healthy mucosa is protected from contact with potentially harmful bacteria like *Bacteroides, Entero-bacteriaceae, Enterococci, and Clostridium difficile* by an impenetrable highly viscous mucus barrier.

Inflammatory bowel disease is a polymicrobial infection that is characterized by a sustained broken mucus barrier with subsequent bacterial migration toward mucosa and proliferation of complex bacterial biofilms on the epithelial surface, cytopathologic effects and infiltration of submucosa.

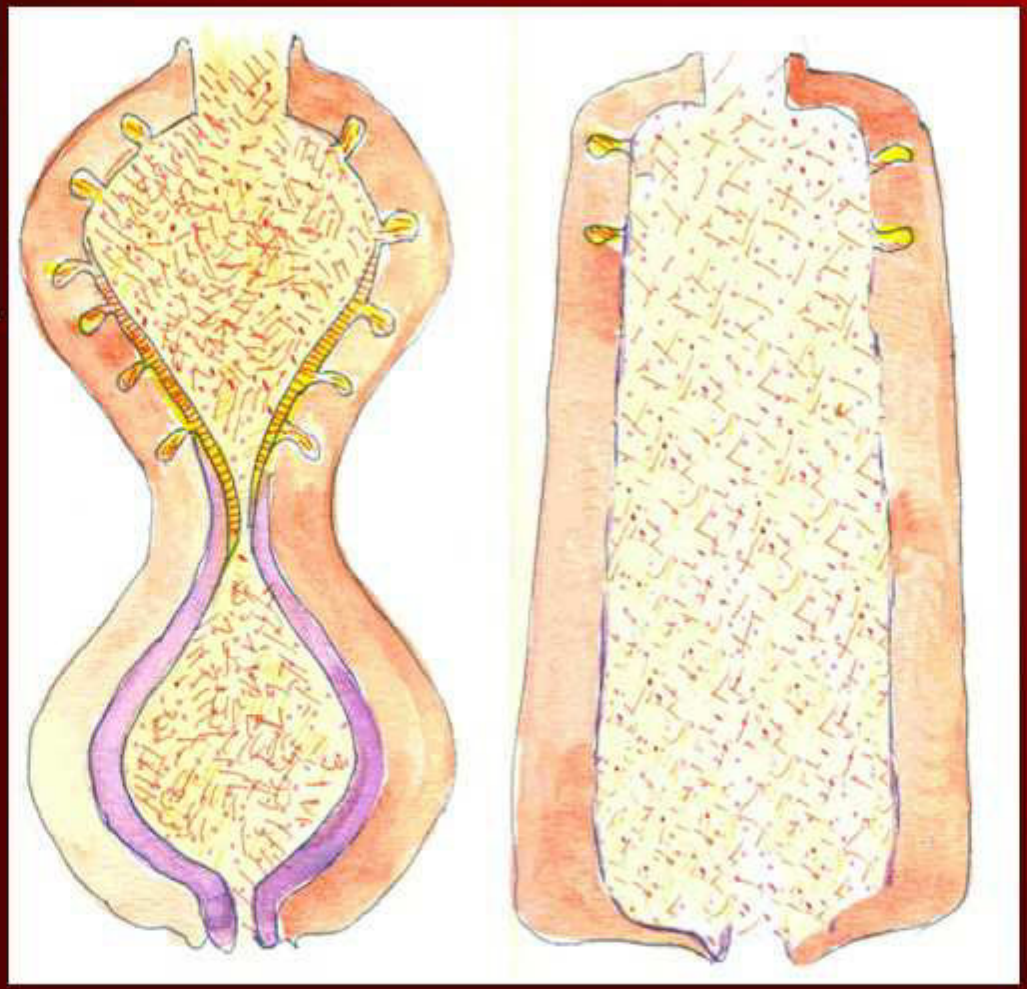
Hygiene hypothesis



Kochen mit dem WOK

Indien, **Mini Auberginen,**
Südafrika, **Mini Zucchini,**
Peru, **Mini Spargel grün oder**
Kenia, **Kaiserschoten**
Kl. I, 100 g = 1.00, je 200-g-Packung

1.99



Soaps and emulsifying substances make our environment clean.
They may however have the same effect on the mucus of man
as DSS on the mucus of mouse.

Factors affecting mucus barrier

Exogenic:

Detergents:

Bacterial virulence:

Glutens as natural emulsifiers need bacteria to be pathogenetic

Smoking

Endogenic:

Bile acids are normally fully resorbed in ileum but lead to diarrhea if arrive in large intestine

Defensins, Antibodies draining

Probiotics, Prebiotics,

Oligonucleotids Nucleinacidsderivates

Inflammatory response

Genetic

NOD 2 Mutation

EU admitted emulsifiers

E425, Konjak
E432 bis E436, Polysorbat
- E432, Polyoxyethylen-sorbitan-monolaurat (Polysorbat 20)
- E433, Polyoxyethylen-sorbitan-monooleat (Polysorbat 80)
- E434, Polyoxyethylen-sorbitan-monopalmitat (Polysorbat 40)
- E435, Polyoxyethylen-sorbitan-monostearat (Polysorbat 60)
- E436, Polyoxyethylen-sorbitan-tristearat (Polysorbat 65)

E440, Pektine, Amidiertes Pektin
E442, Ammoniumsalze von Phosphatidsäuren
E444, Saccharose-acetat-isobutyrat
E445, Glycerinester aus Wurzelharz/Kolophonester
E450 bis E452, Phosphate
E459, Beta-Cyclodextrin
E460 bis E469 Cellulose und Celluloseverbindungen
- E460, Cellulose, Mikrokristalline Cellulose, Cellulosepulver
- E461, Methylcellulose
- E463, Hydroxypropylcellulose
- E464, Hydroxypropylmethylcellulose
- E465, Ethylmethylcellulose
- E466, Carboxymethylcellulose, Natriumcarboxymethylcellulose
- E468, Vernetzte Natrium-Carboxymethylcellulose
- E469, Enzymatisch hydrolysierte-Carboxymethylcellulose

E470a und E470b, Salze von Speisefettsäuren
- E470a, Natrium-, Kalium- und Calciumsalze von Speisefettsäuren
- E470b, Magnesiumsalze von Speisefettsäuren

E471 bis E472f, Mono- und Diglyceride von Speisefettsäuren
- E471, Mono- und Diglyceride von Speisefettsäuren, Monoglycerid
- E472a, Essigsäureester von Mono- und Diglyceriden von Speisefettsäuren
- E472b, Milchsäureester von Mono- und Diglyceriden von Speisefettsäuren
- E472c, Citronensäureester von Mono- und Diglyceriden von Speisefettsäuren
- E472d, Weinsäureester von Mono- und Diglyceriden von Speisefettsäuren
- E472e, Mono- und Diacetylweinsäureester von Mono- und Diglyceriden von Speisefettsäuren
- E472f, Gemischte Essig- und Weinsäureester von Mono- und Diglyceriden von Speisefettsäuren

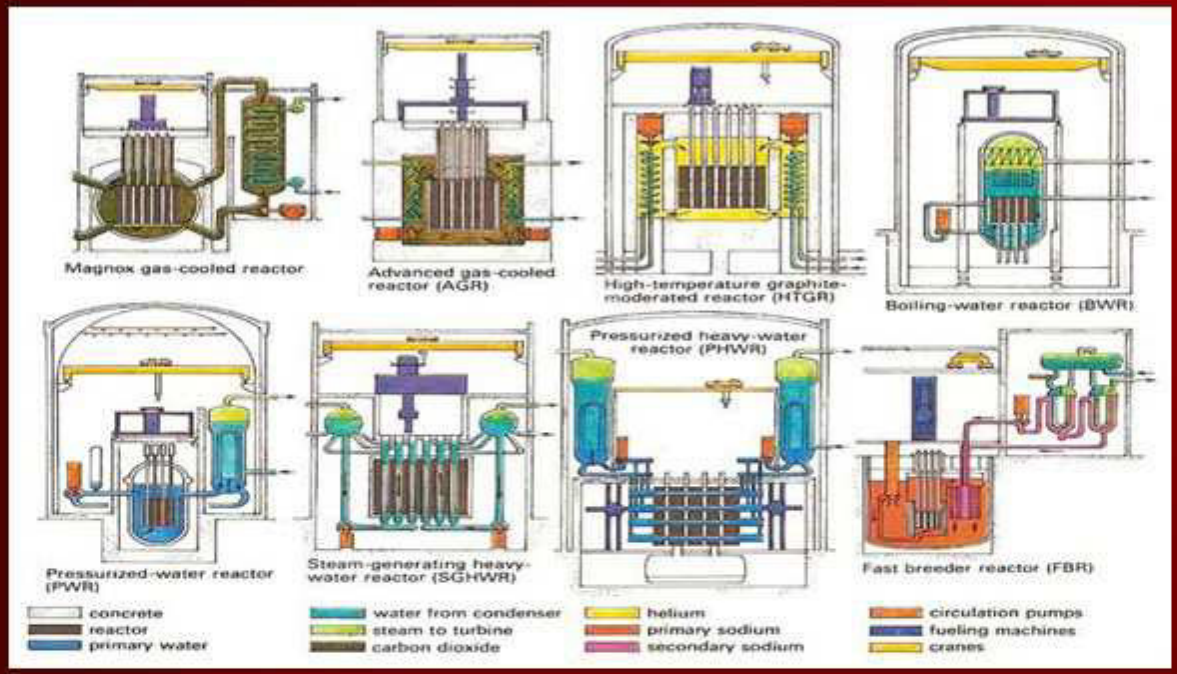
E473, Zuckerester von Speisefettsäuren
E474, Zuckerglyceride
E475, Polyglycerinester von Speisefettsäuren, Polyglycerinester
E476, Polyglycerin-Polyricinoleat
E477, Propylenglycolester von Speisefetten
E479, Thermooxidiertes Sojaöl mit Mono- und Diglyceriden von Speisefettsäuren
E481 bis E483, Natriumstearoyl-2-lactylat, Calciumstearoyl-2-lactylat, Stearyltartrat
E491bis E495, Stearin- und Palmitatverbindungen

Possible ways to remodel the mucus barrier

- Selective control of mucus secretion and dehydration
  (analoga of cortisol)
  Induction of a higher differentiation of epithelial cells, which leads to switch from mainly secretary to adsorptive function
  (analoga of anti TNF suppressing apoptosis, MTX, Azathioprin?)
- Suppression of adherent bacterial biofilms
  (effects of 5-ASA)
- Reduction of the burden of detergents and emulsifiers in our foods
- (Colestyramin, Ursofalk)
- Eradication of occasional pathogens comprising mucus barrier
  like Entero-adhesive E.coli, Fusobaterium nucleatum, Serpulina
  (antibiotics, probiotics?)
- Simulation of innate immunity
  (GM CSF, Interferon, probiotics?)

. Regulation of CNS (Amitriptylin) and local neuronal control (Imodium)

Do single isotopes/composition within nuclear plant determine its work?

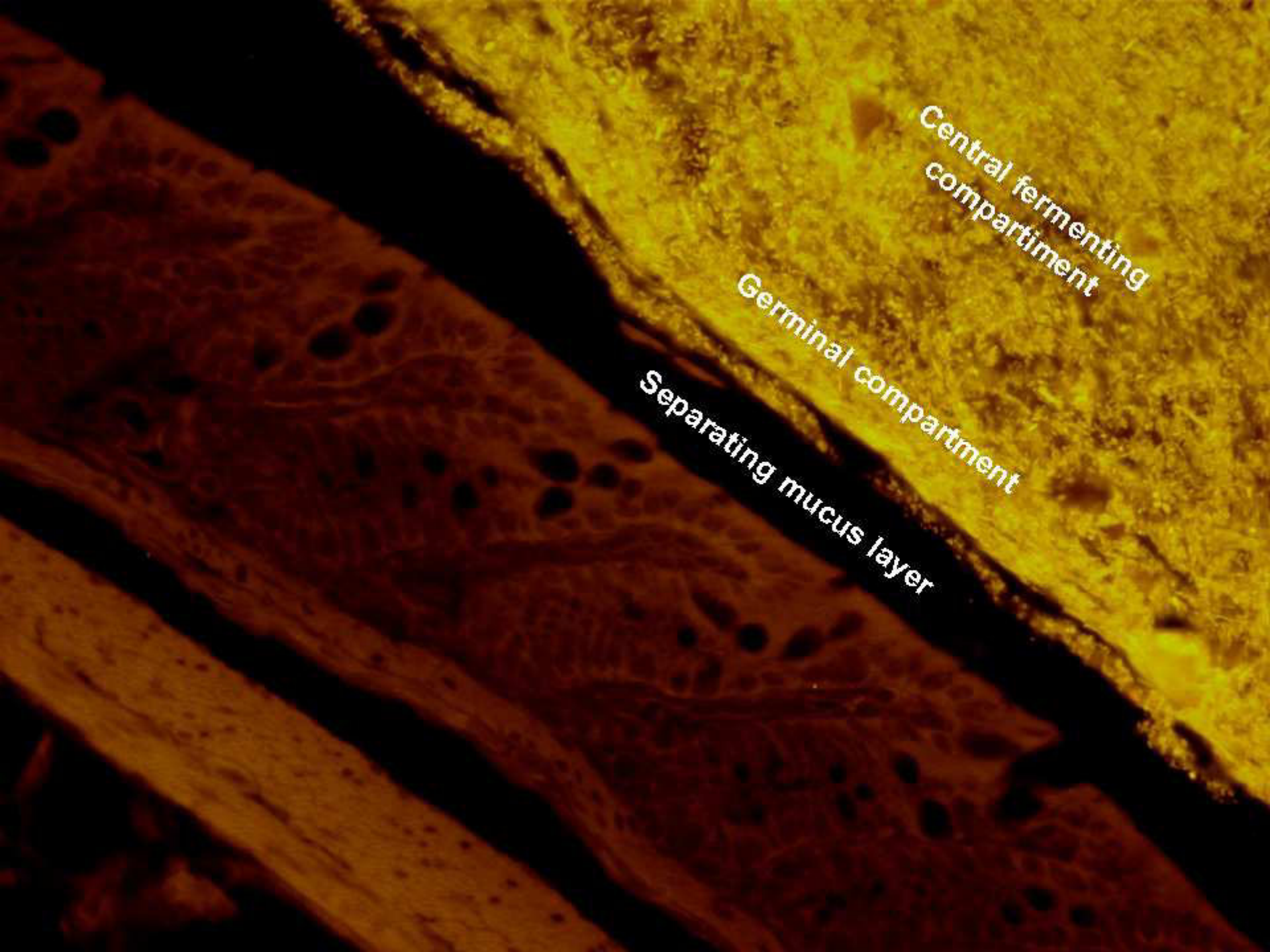


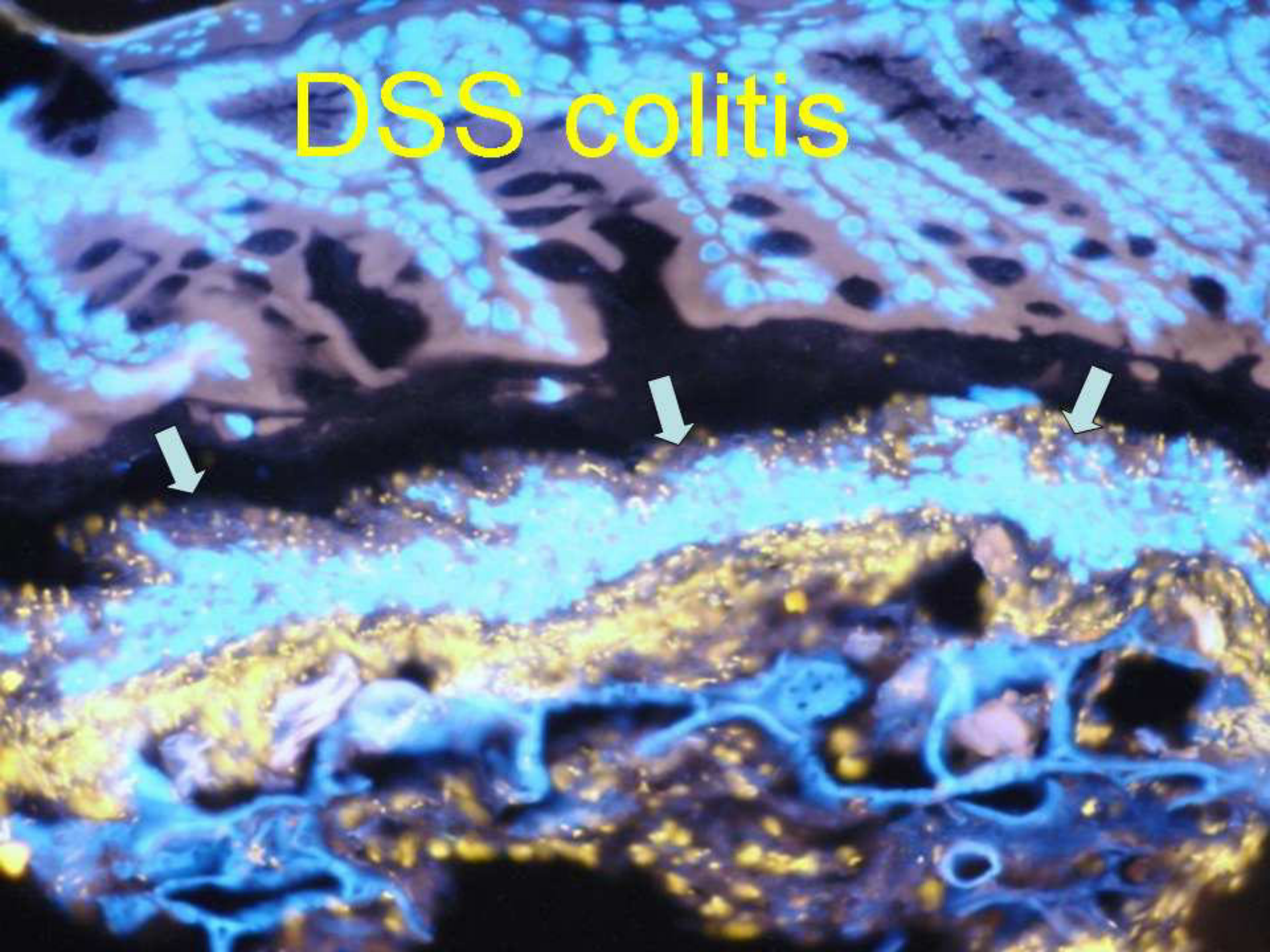
Can the composition of bacteria inside bioreactor help us to understand it?

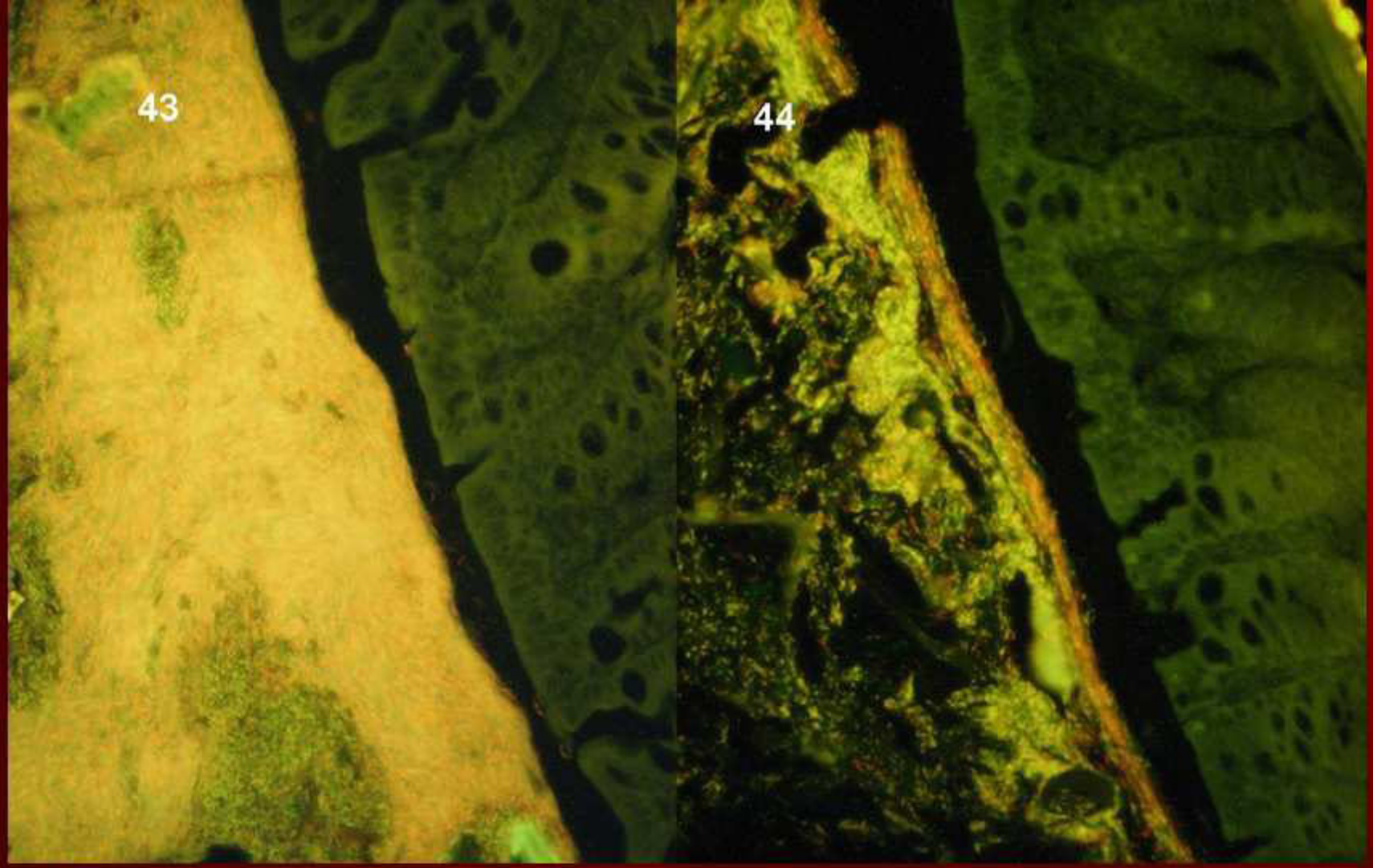
To understand how the colonic bioreactor works we need interventional studies deliberately changing biochemical power of the bioreactor and monitoring its composition.

Combination of antibiotics together with Sacharomyces boullardii is a perfect tool for this purpose.

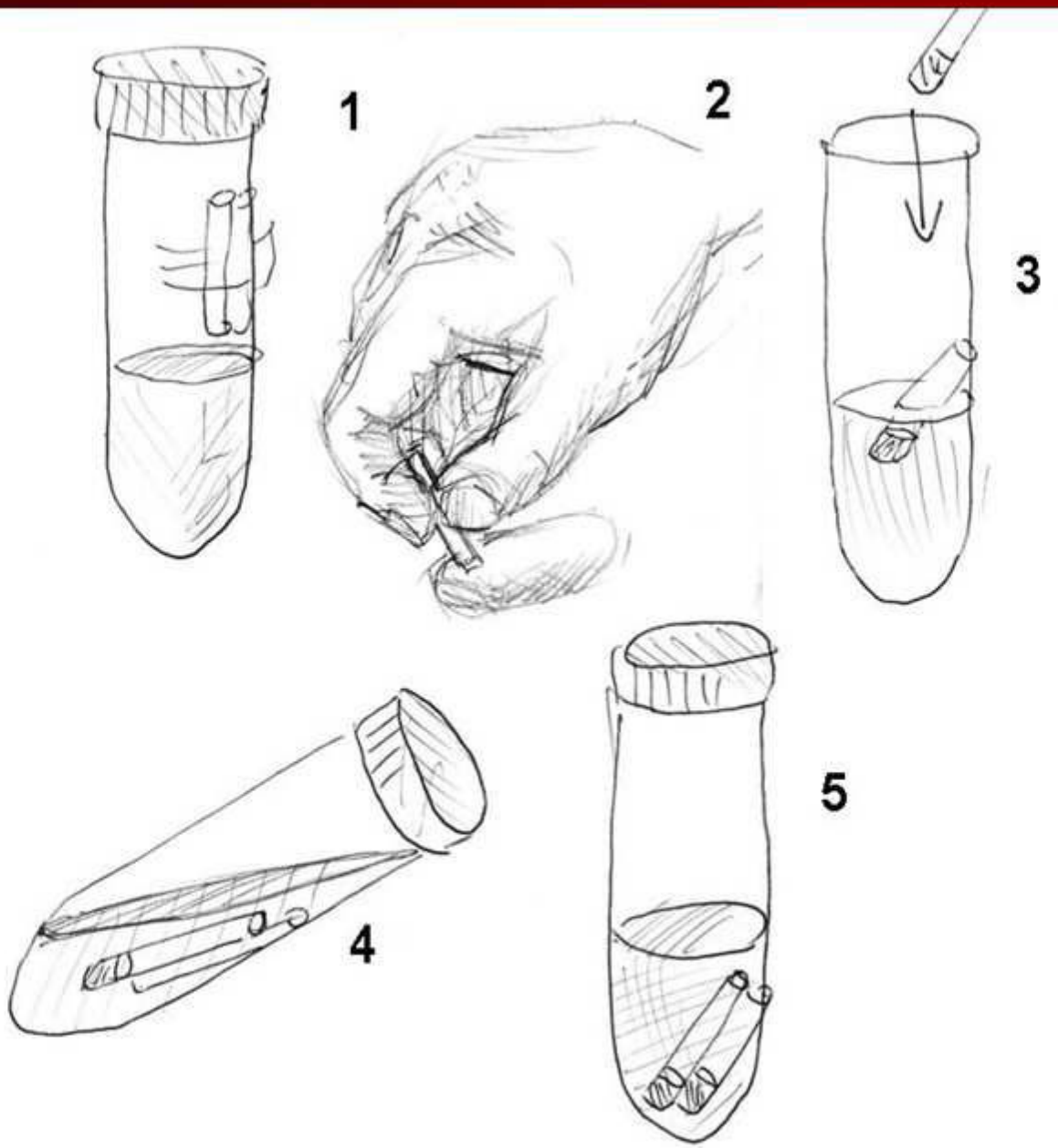
- Structure-functional compartment analysis of colonic microbiota

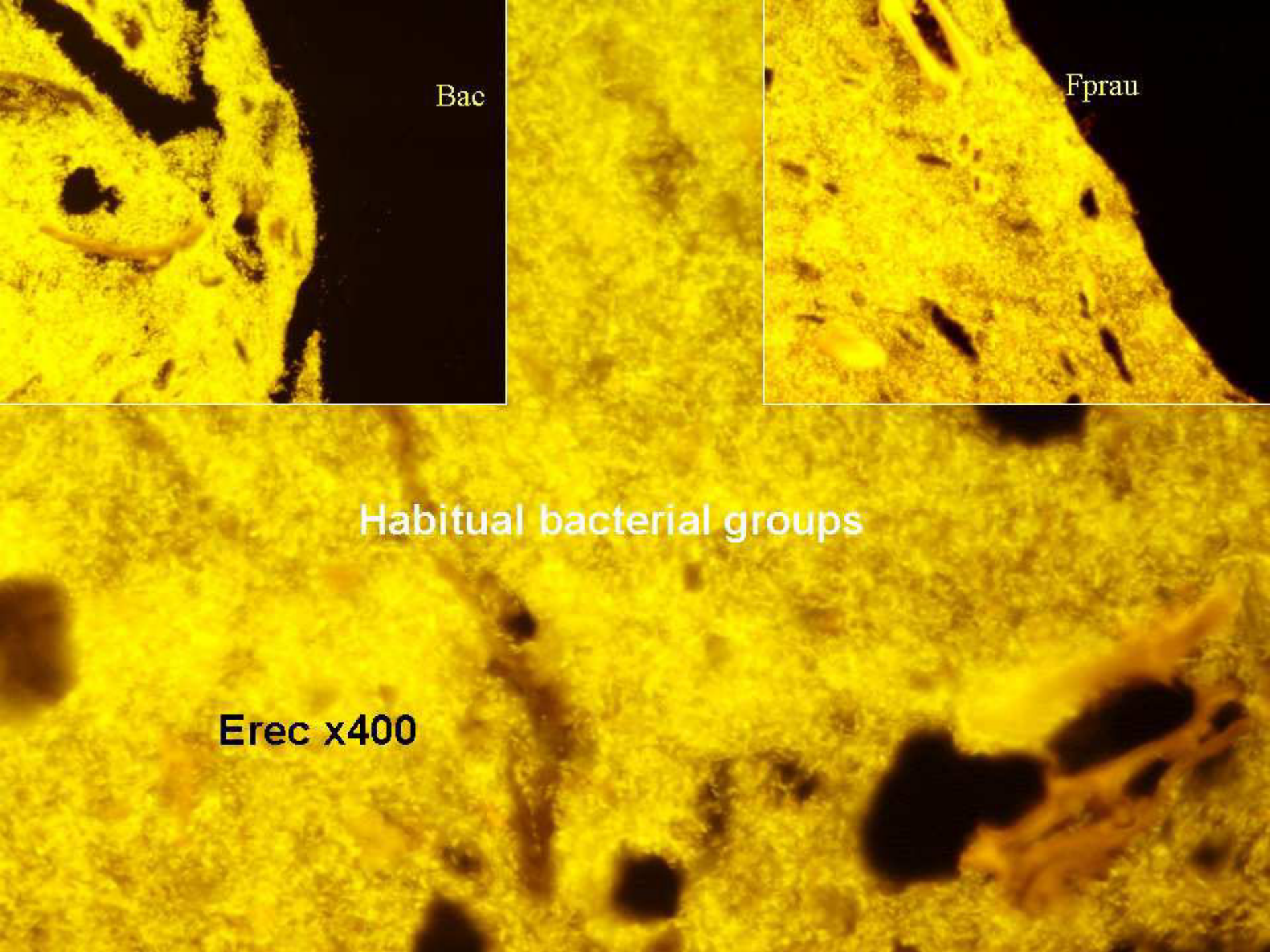

Central fermenting compartiment
Germinal compartment
Separating mucus layer

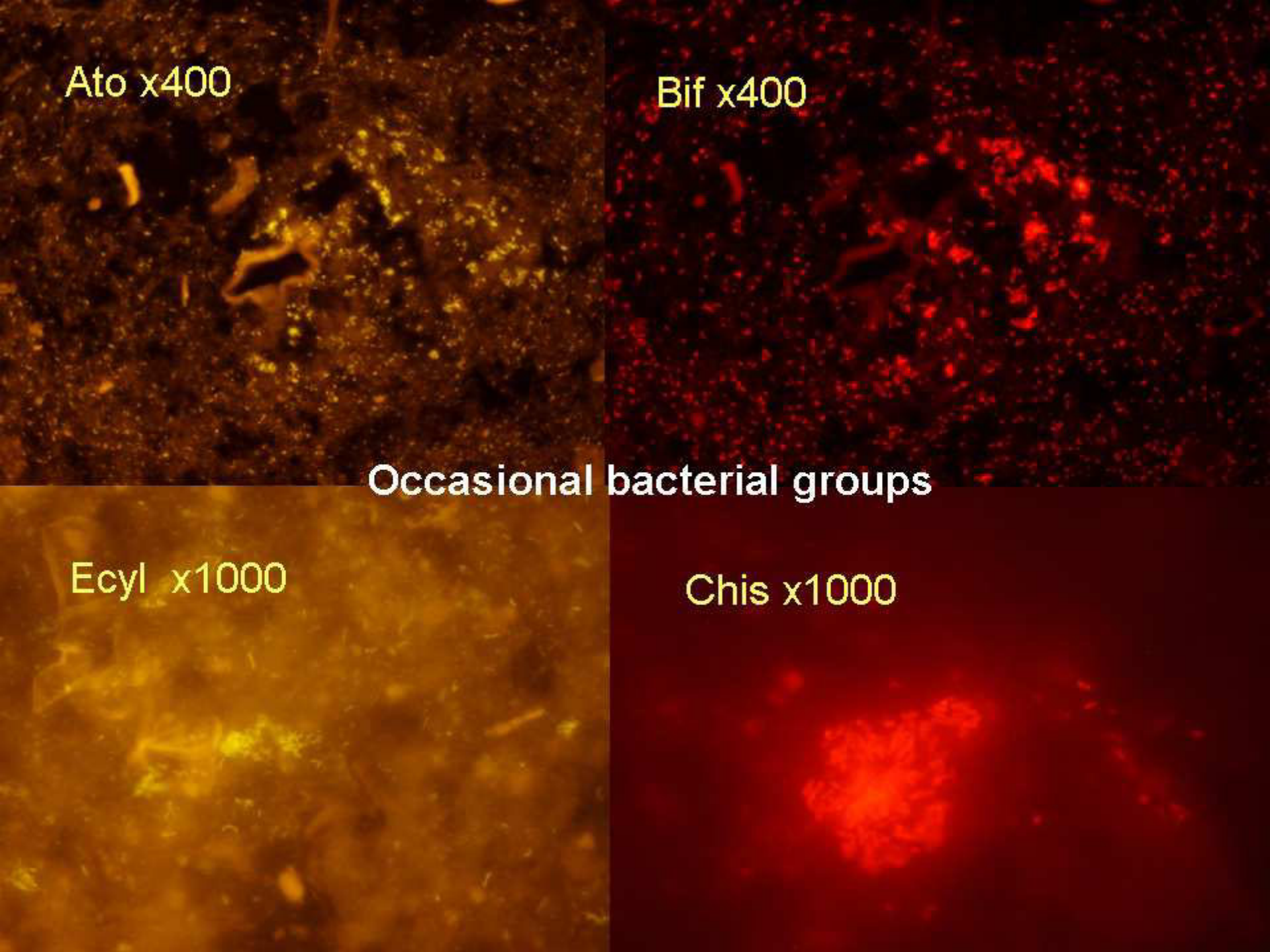

DSS colitis



- Colonic bacteria in the healthy wild-type mouse are diffusely distributed and have similar high concentrations at the center of feces and in the “germinal” zone.
- Bacteria are suppressed in a 28 week-old mouse with IL-10 deficiency, especially at the center of feces. The germinal zone is not involved.


1
2
3
4
5

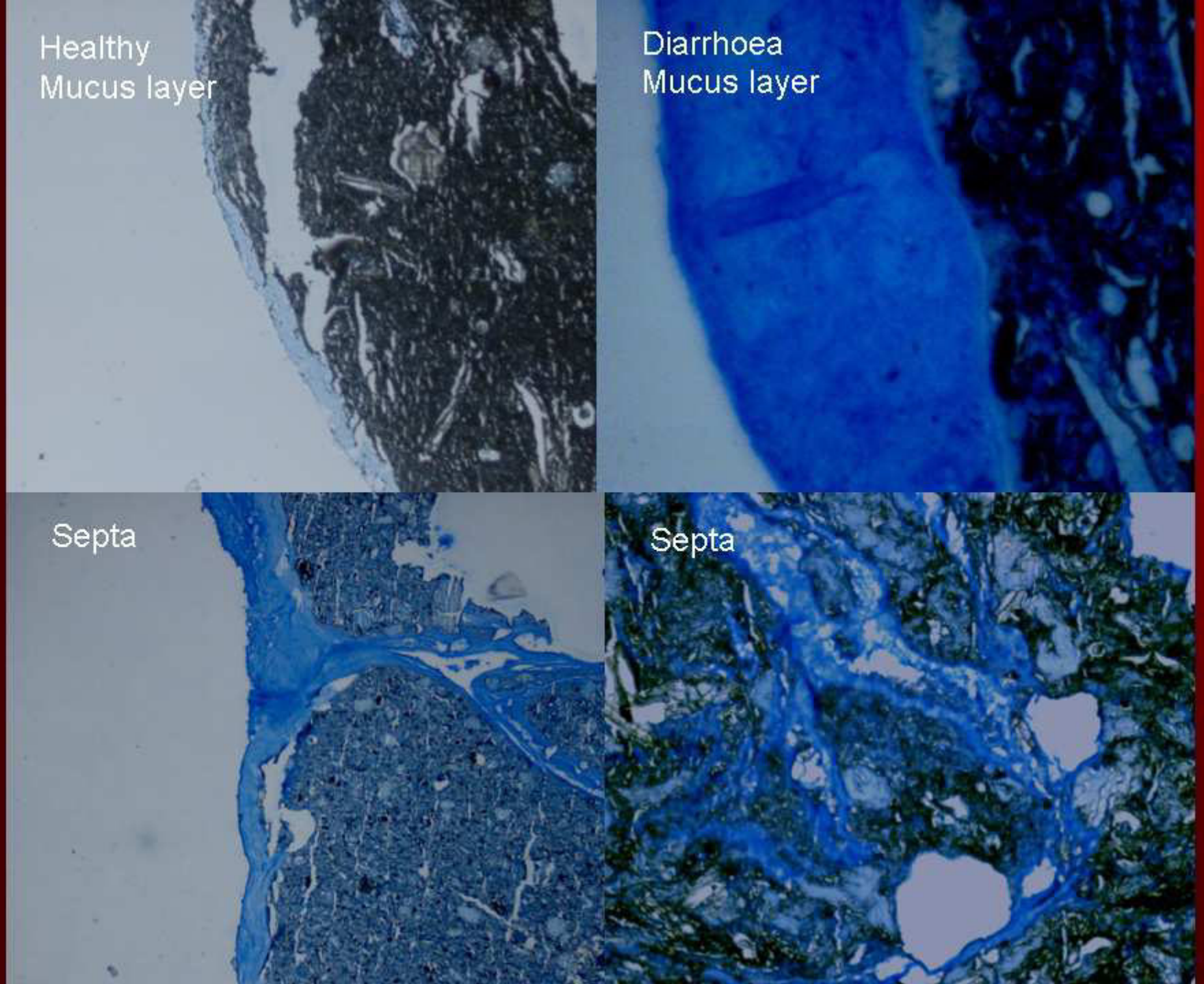

Bac
Fprau
Habitual bacterial groups
Erec x400


Ato x400
Bif x400
Occasional bacterial groups
Ecyl x1000
Chis x1000

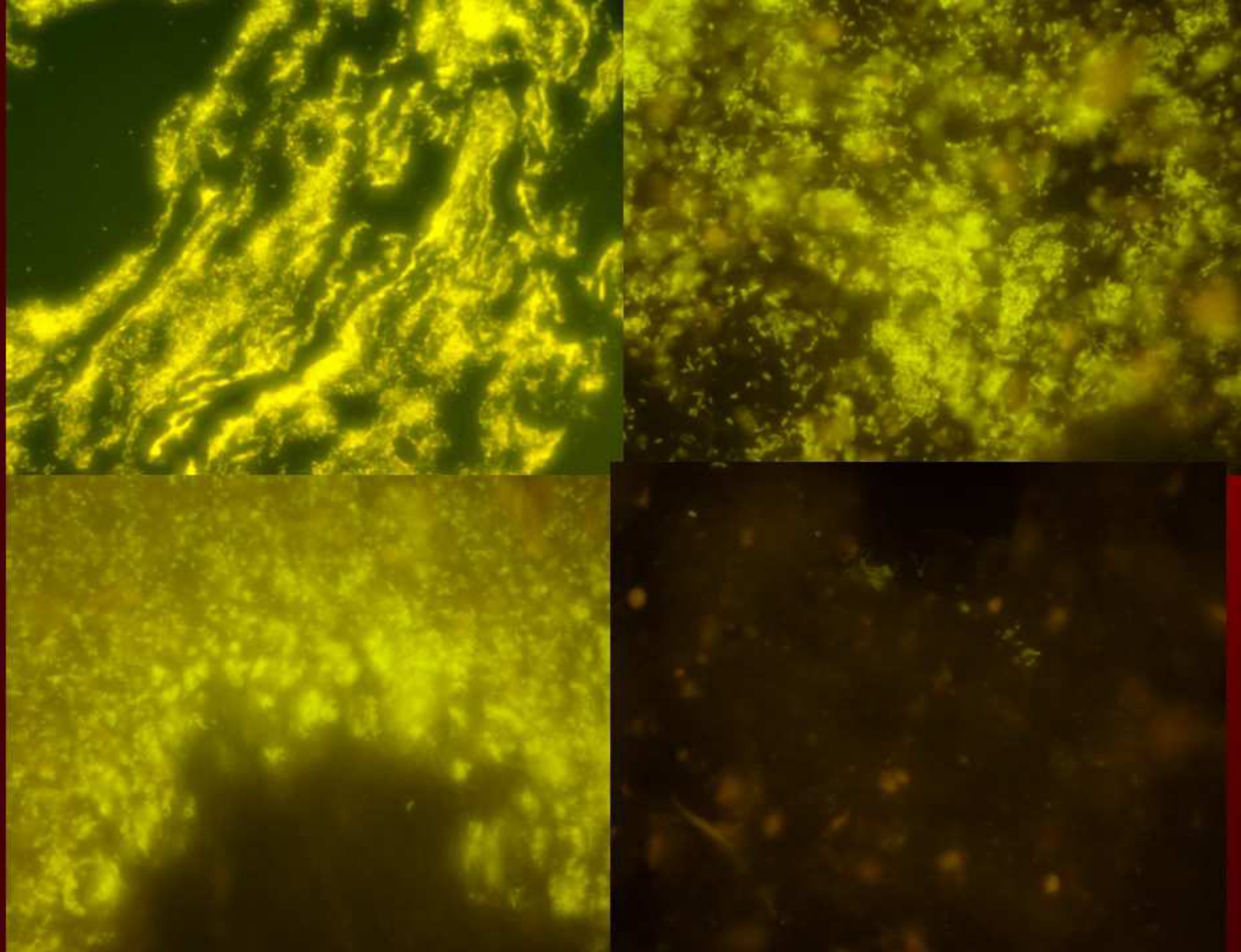
- Protection
- Purging
- Decontamination
- Restocking

- **Protection**

- Mucus thickening,
- Flatulence,
- colic

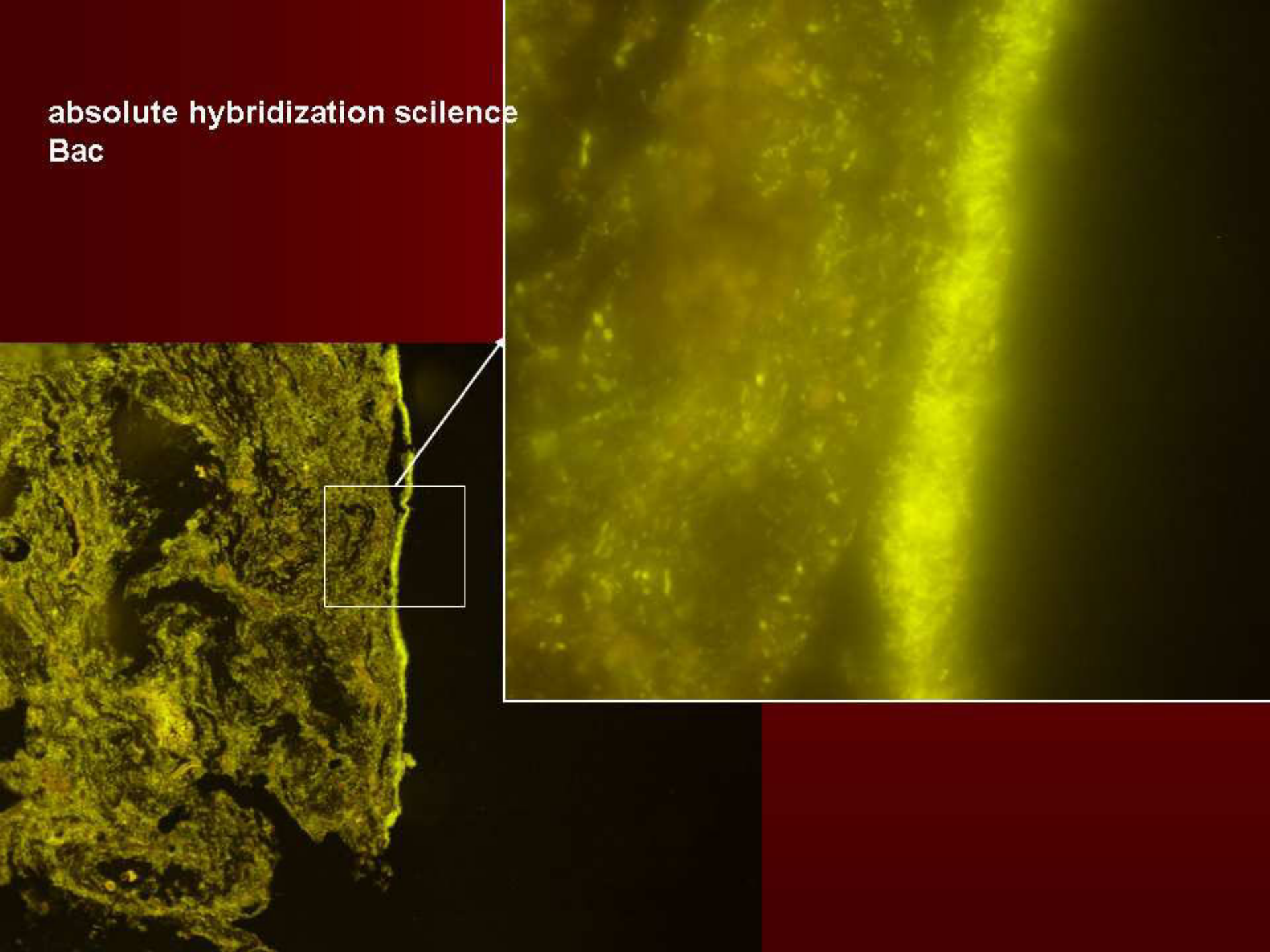

Healthy
Mucus layer
Diarrhoea
Mucus layer
Septa
Septa

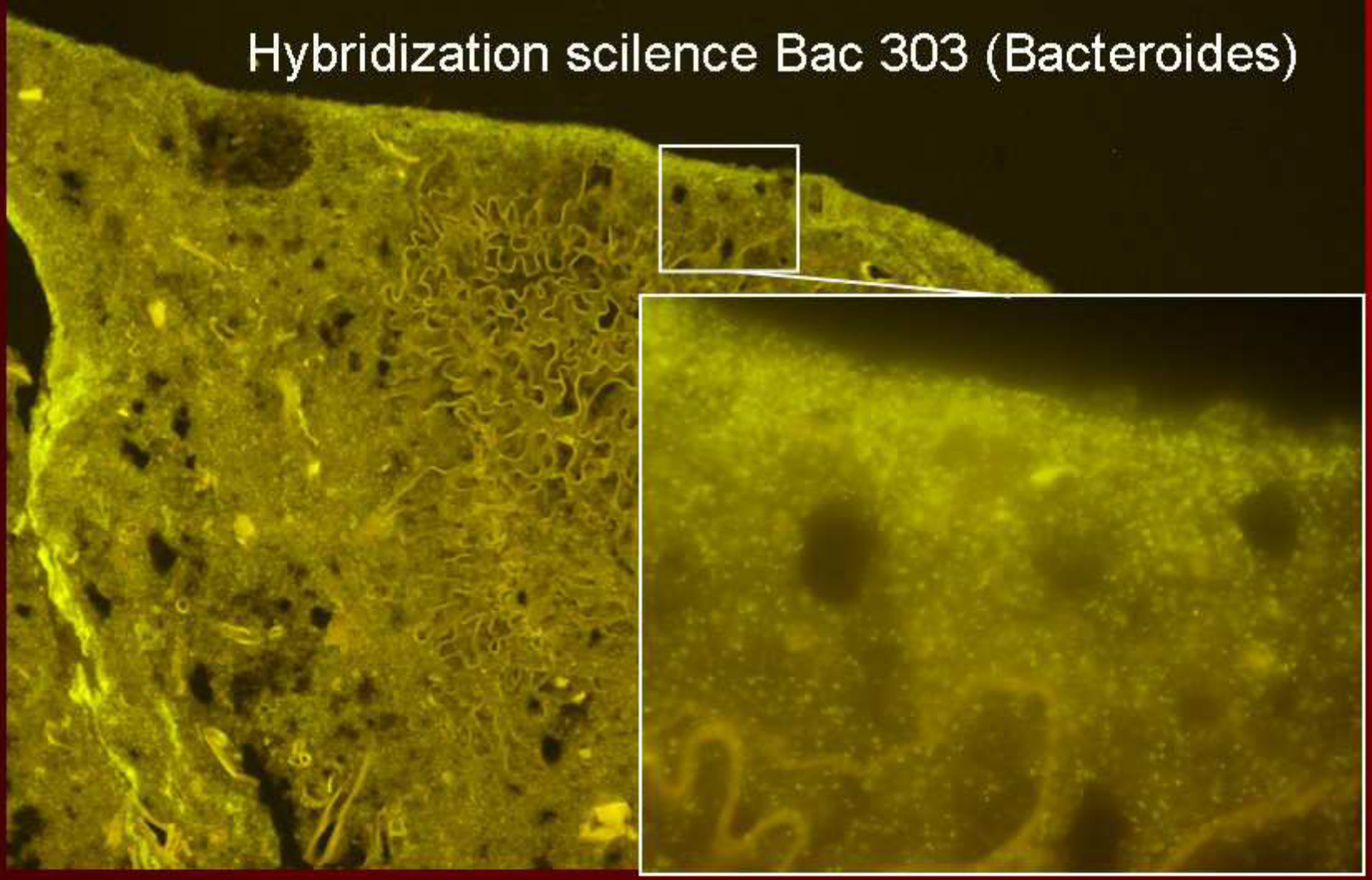
- Purging
- (destructuring of the habitual bacterial groups)



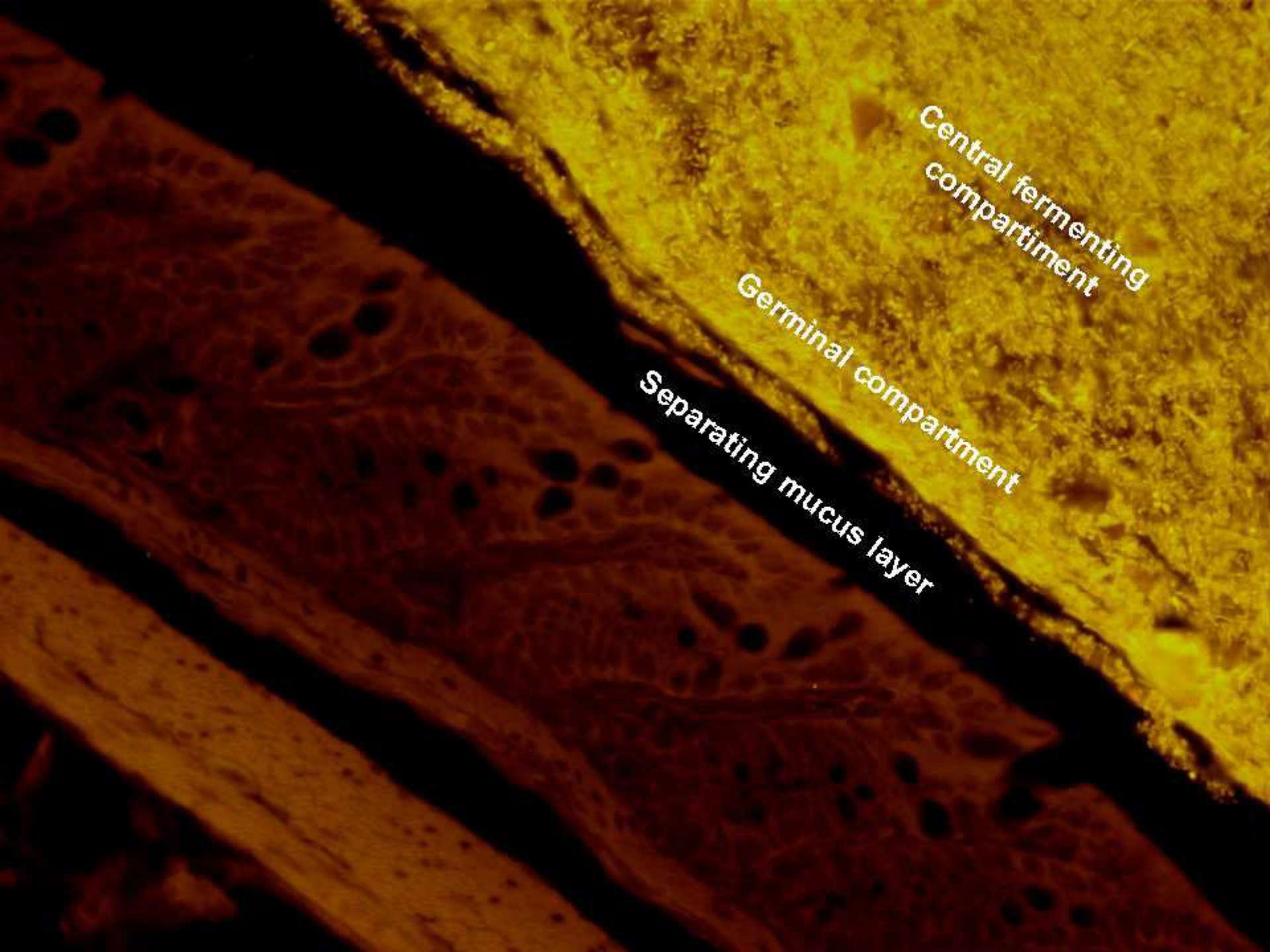
- **Decontamination**
- (Hybridization silence or supression of habitual bacterial groups)

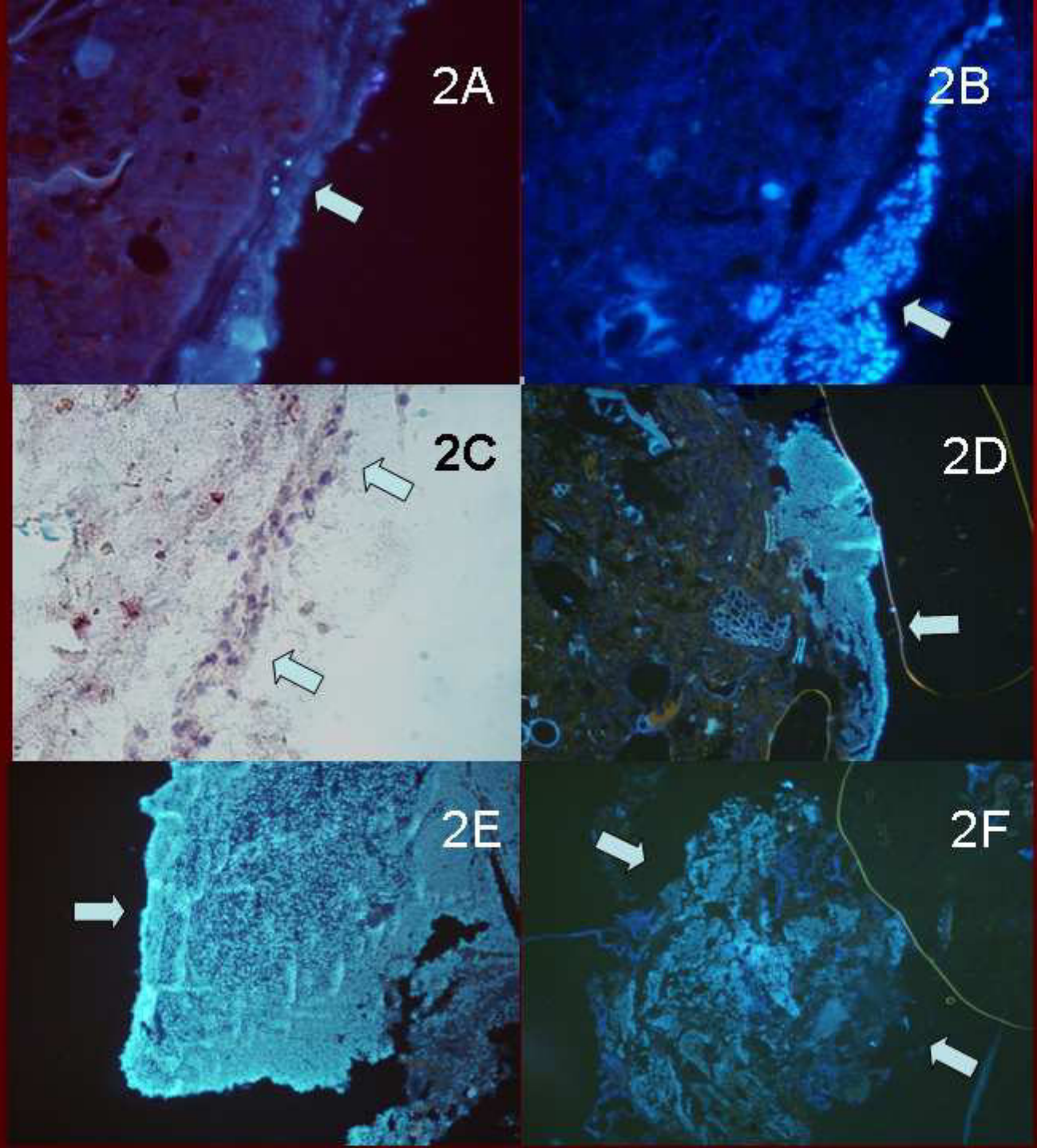
absolute hybridization scilence
Bac




Hybridization scilence Bac 303 (Bacteroides)

IBD


Central fermenting compartiment
Germinal compartment
Separating mucus layer


2A
2B
2C
2D
2E
2F

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