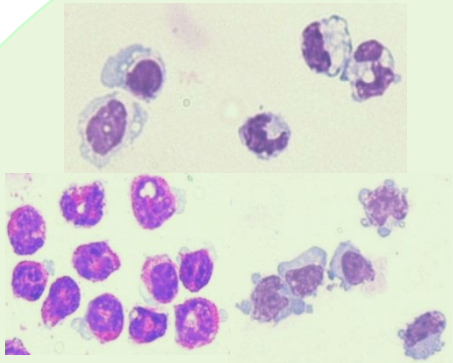
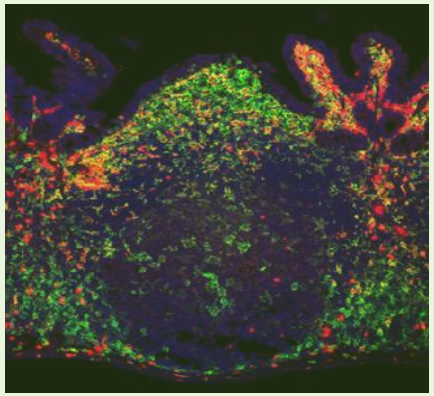
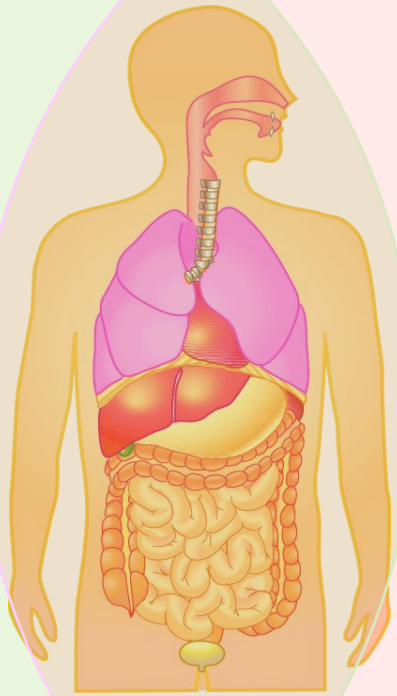
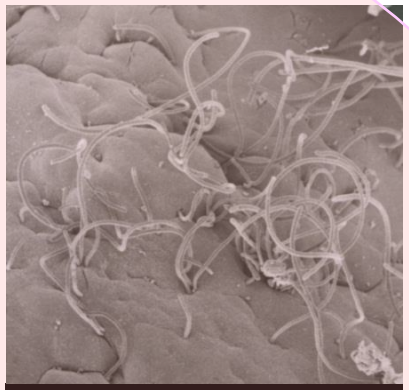
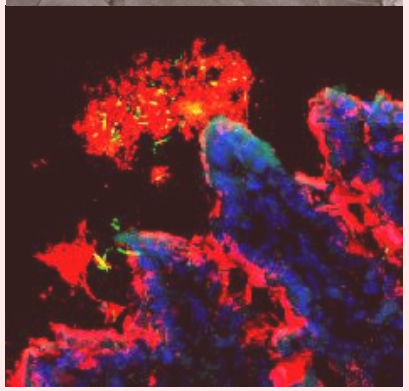
The mechanism of intestinal epithelial glycosylation and regulation of gut homeostasis











Division of Molecular Immunology, Medical Mycology Research Center, Chiba University

International Research and Development Center for Mucosal Vaccines,

The Institute of Medical Science, The University of Tokyo

Yoshiyuki Goto

Today's topics

1. Interplay between commensal microorganisms and host immune system

2. Induction of intestinal epithelial glycosylation and phylaxis

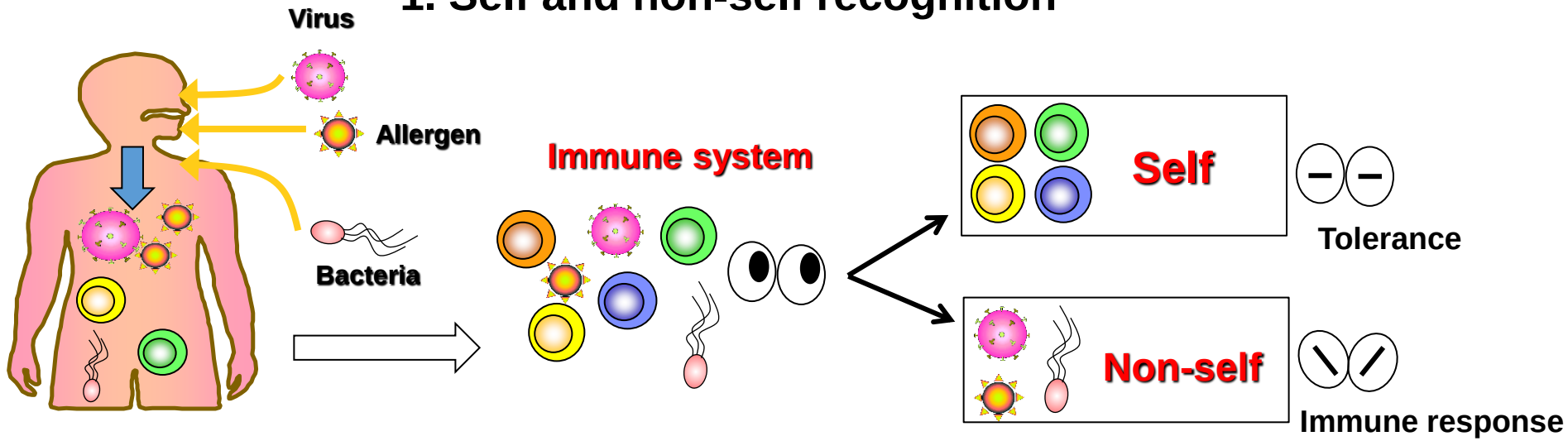
Today's topics

1. Interplay between commensal microorganisms and host immune system

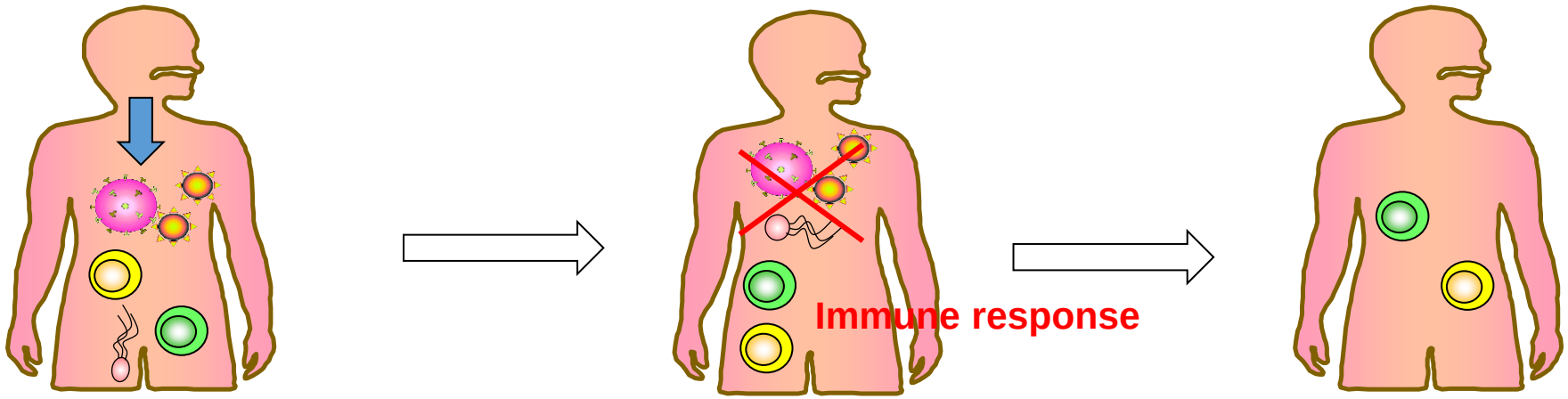
2. Induction of intestinal epithelial glycosylation and phylaxis

What is immune system?

1. Self and non-self recognition



2. Attack non-self antigens



Enigma of Immunology

1. Self and non-self recognition

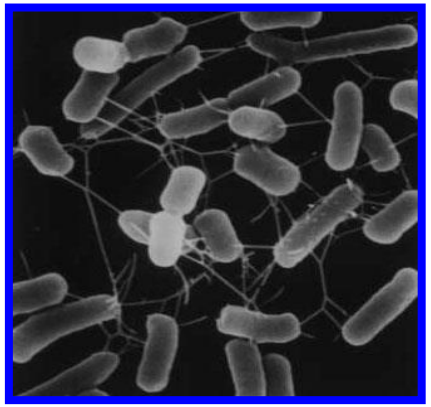
2. Attack non-self antigens

The gut is exposed by various antigens

Food antigens

Tolerance

Commensal bacteria



Symbiosis

Pathogenic bacteria

Elimination

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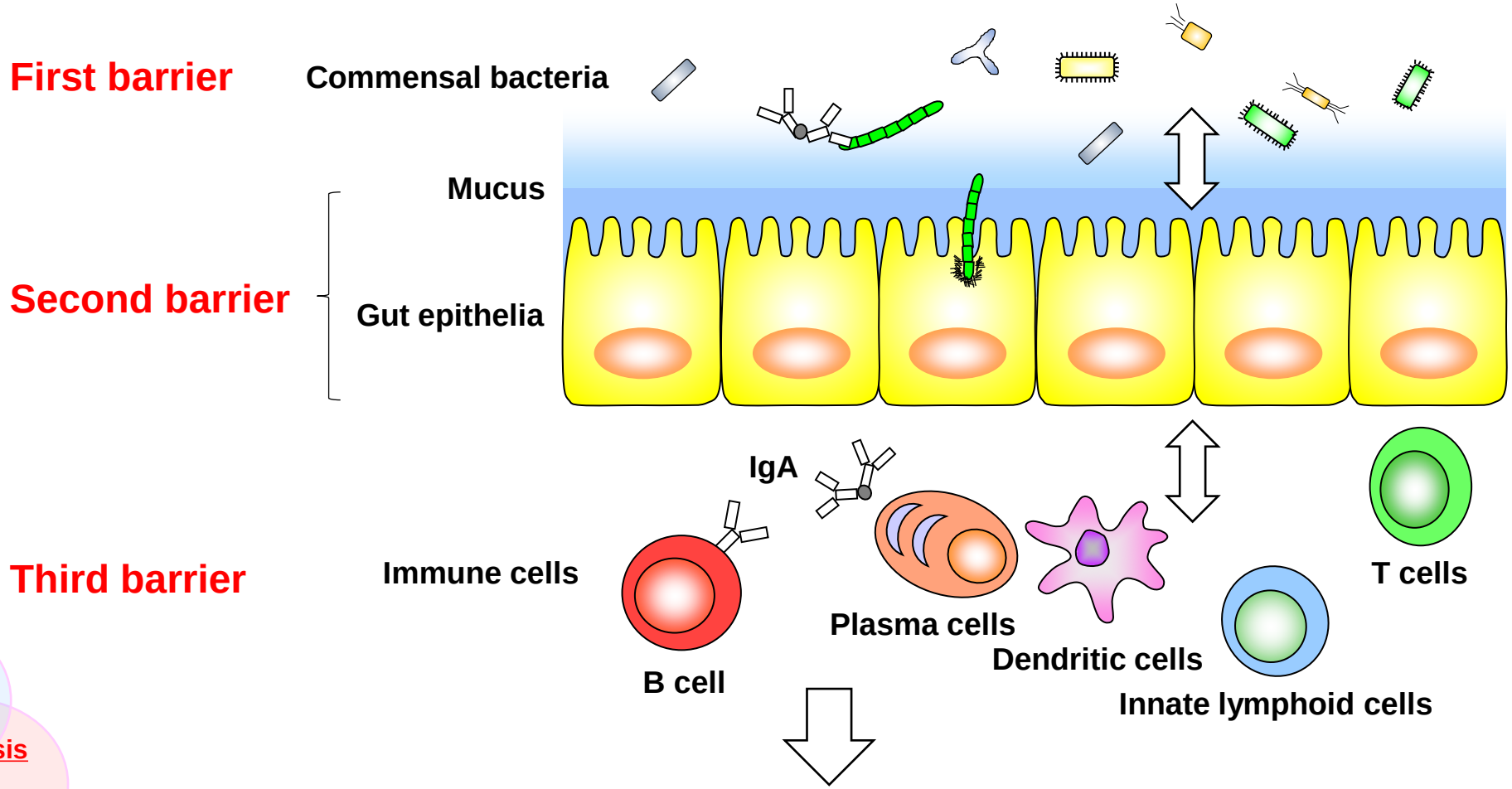
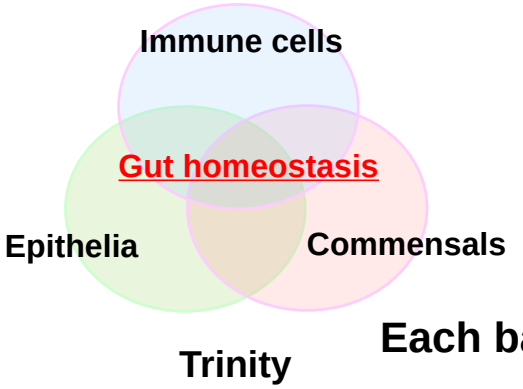
Intestinal immunity

Multi-layered barrier system in the gut





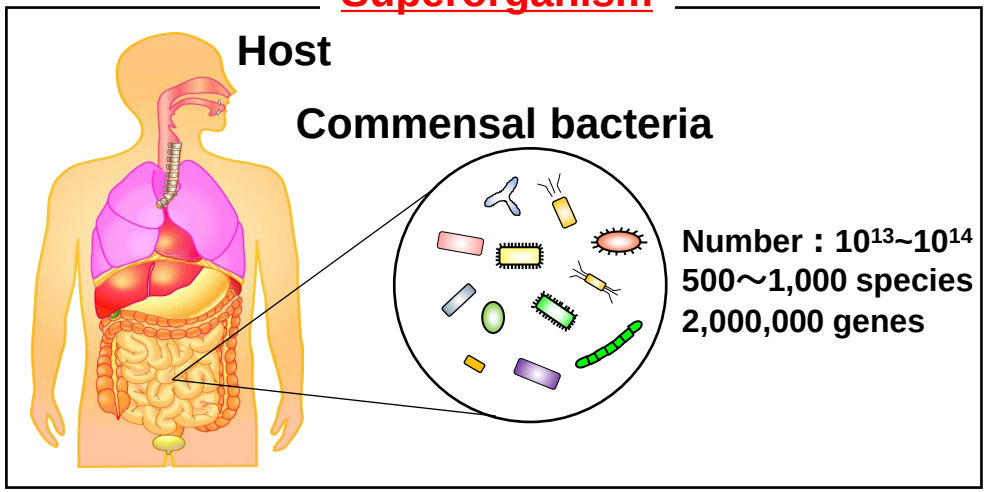
Multi-layered barrier system protect invasion of external antigens

Each barrier system interacts with each other for the maintenance of gut homeostasis

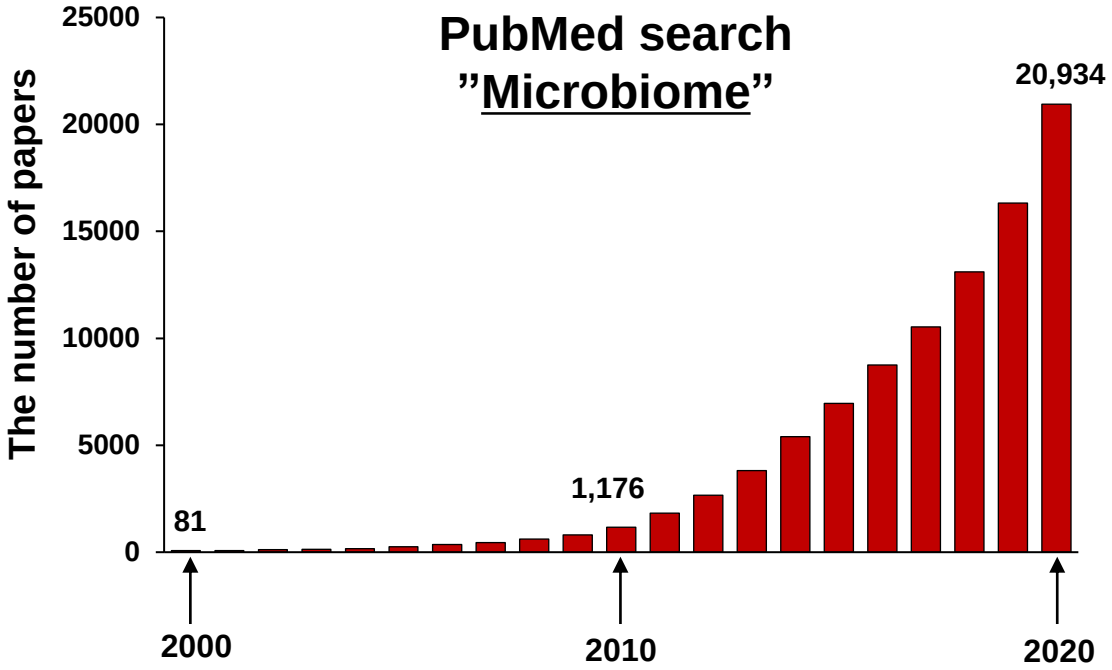
Goto Y. *Front Immunol*. 10:2057, 2019

Commensal microorganisms

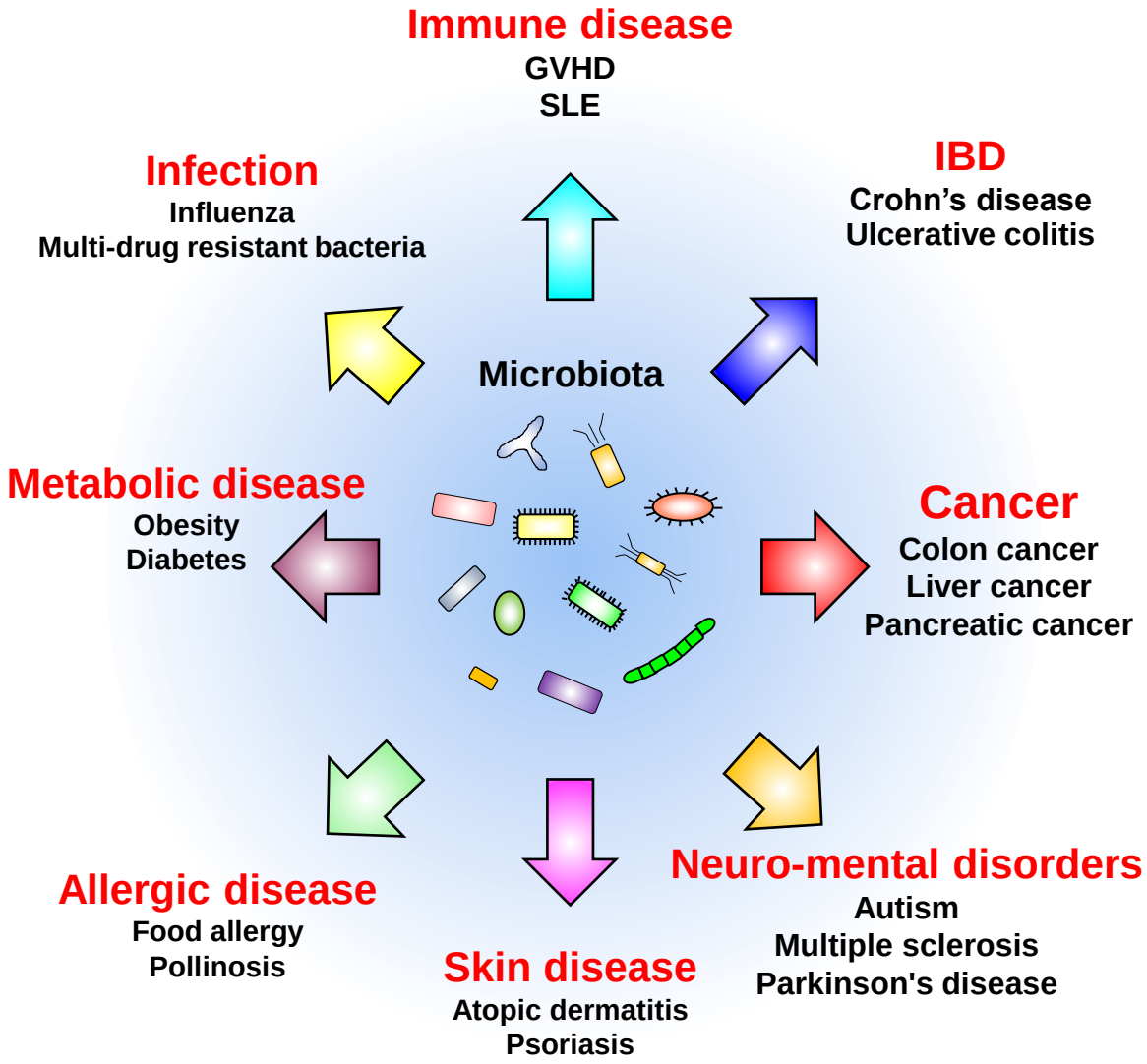
Superorganism



Lederberg J. *Science*, 288 : 287-293, 2000



Commensal bacteria regulate host pathology



Dysbiosis

＝disruption of the homeostasis of gut microbiota

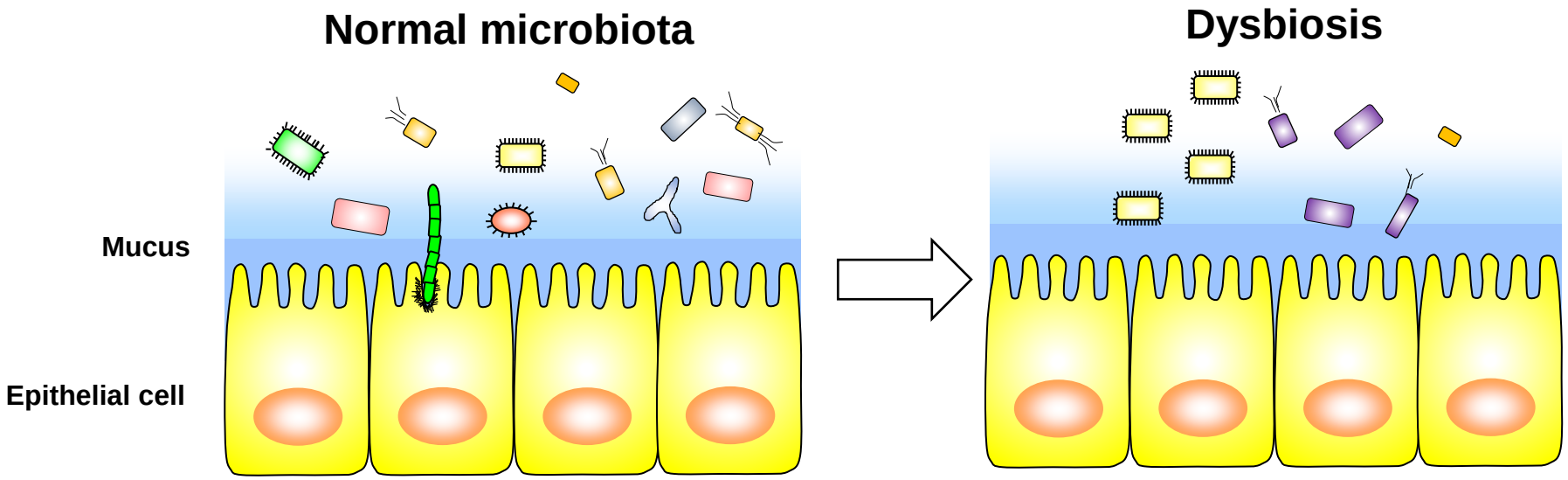
1. Reduction of the species of commensal bacteria
2. Expansion of specific opportunistic bacteria

External factors

1. Antibiotics
2. Food
3. Infection

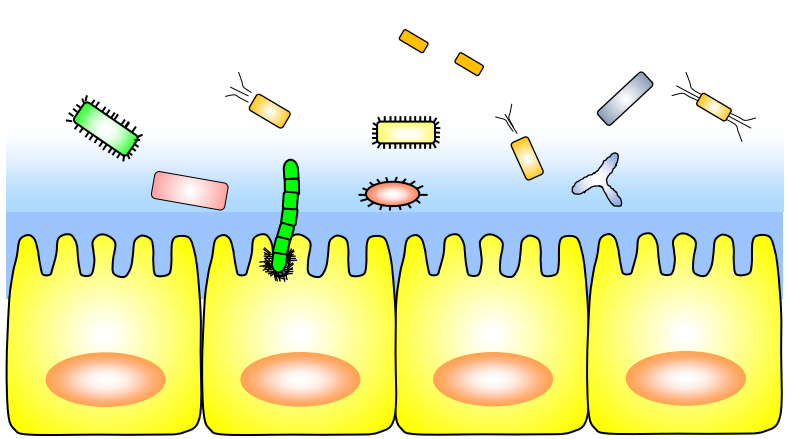
Internal factors

1. Genetic diversity
2. Stress
3. Immune disorder

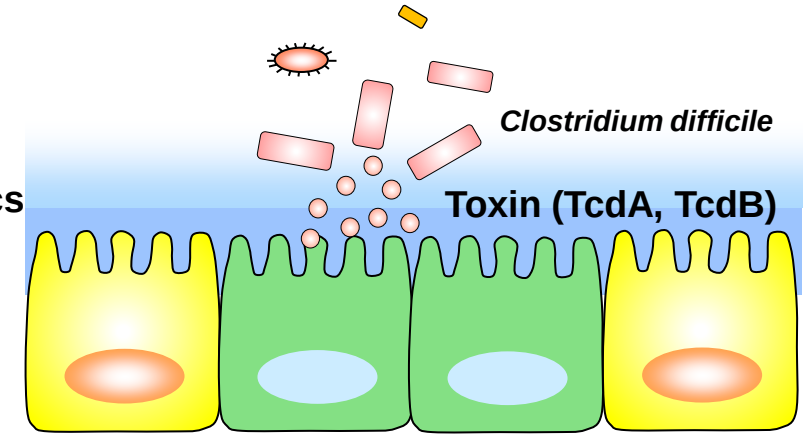


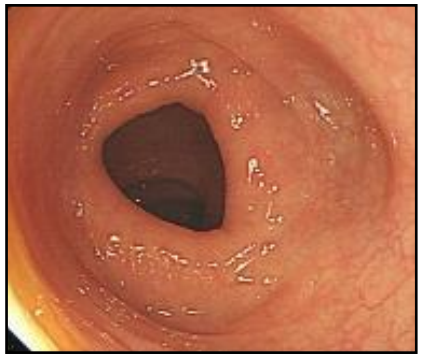
Dysbiosis related infectious disease

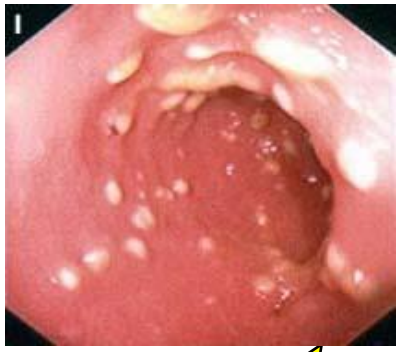
Clostridium difficile infection



Antibiotics



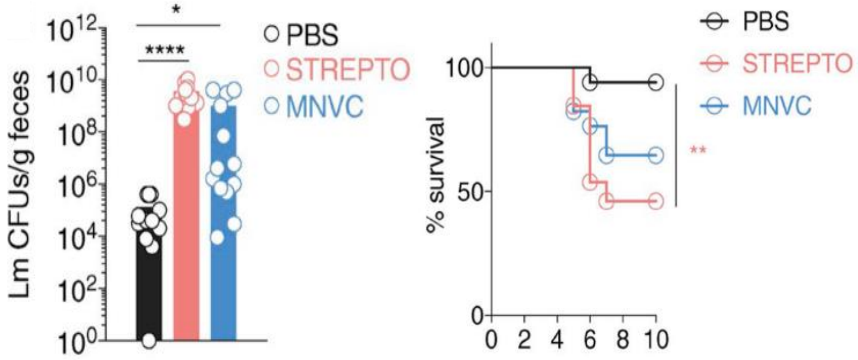




Pseudomembranous enteritis!

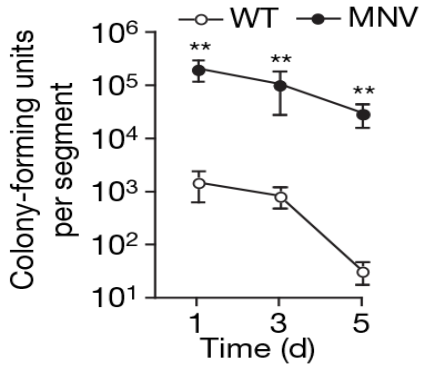
Colonization resistance effects of microbiota

Listeria monocytogenes



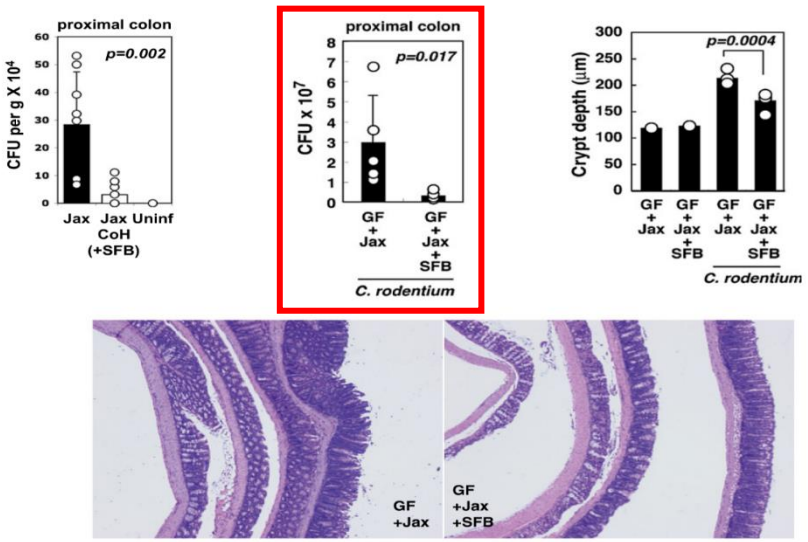
Becattini S, et al. *J Exp Med*. 214: 1973-1989, 2017

Vancomycin-resistant *Enterococcus* (VRE)



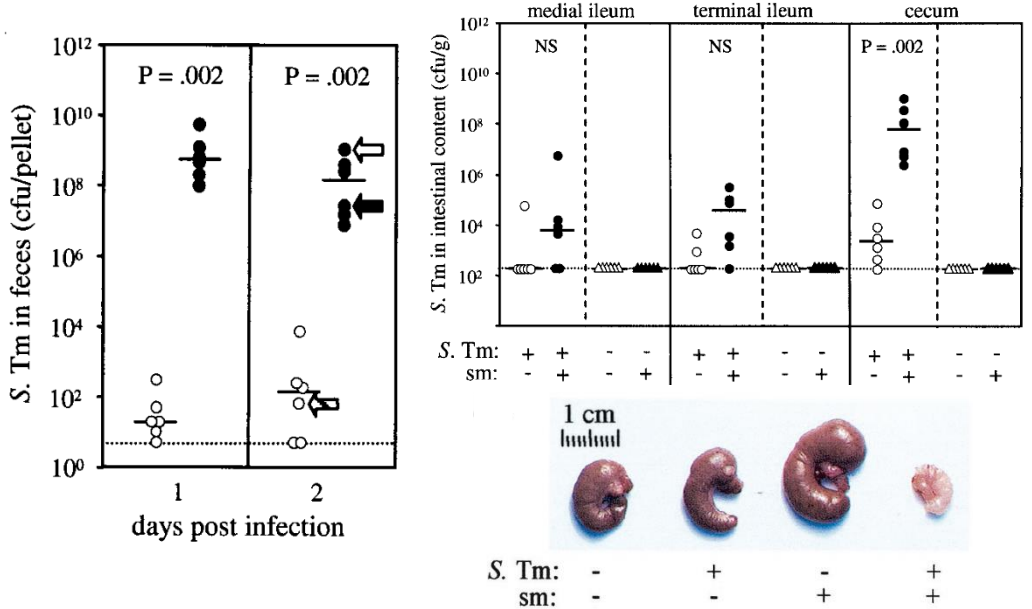
Brandl K, et al. *Nature* 455: 804-807, 2008

Citrobacter rodentium



Ivanov II, et al. *Cell*. 139: 485-498, 2009

Salmonella typhimurium

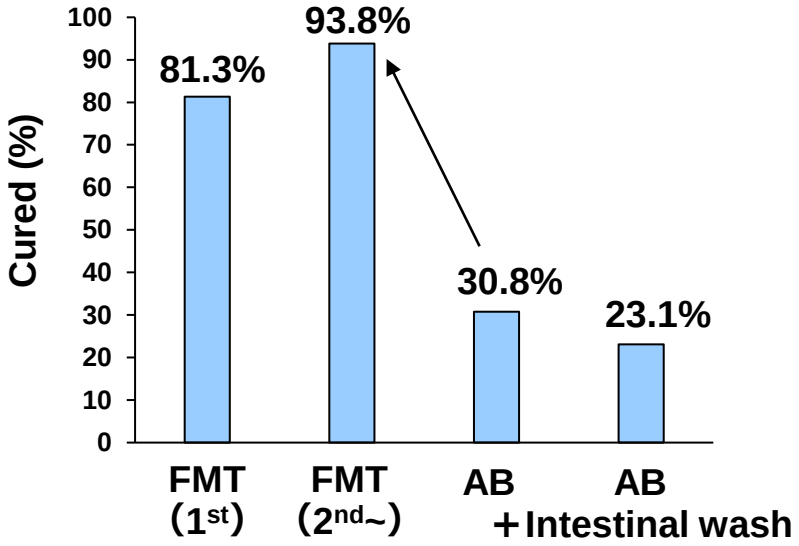


Barthel M, et al. *Infect Immun*. 71: 2839-2858, 2003

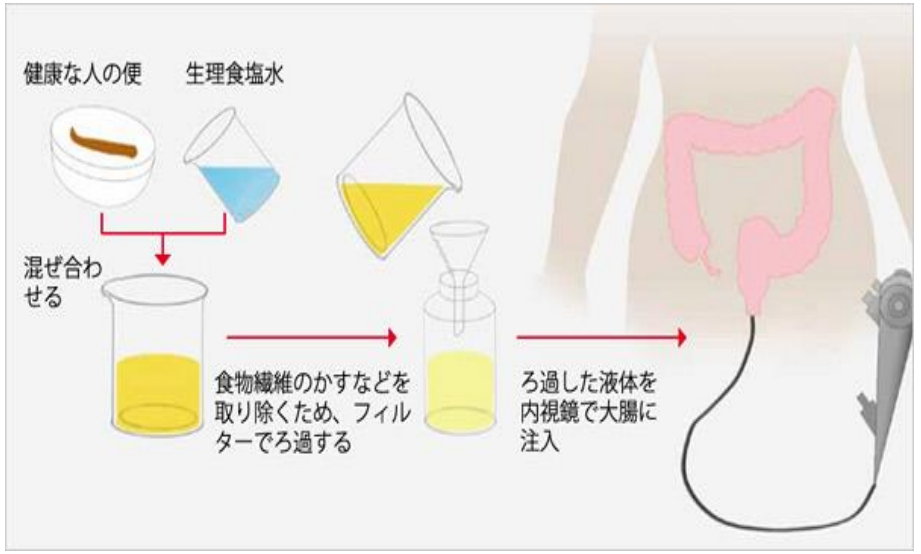
Microbiota-mediated therapeutic approach 1

Fecal Microbiota Transplantation: FMT

Therapeutic effect against *Clostridium difficile* infection



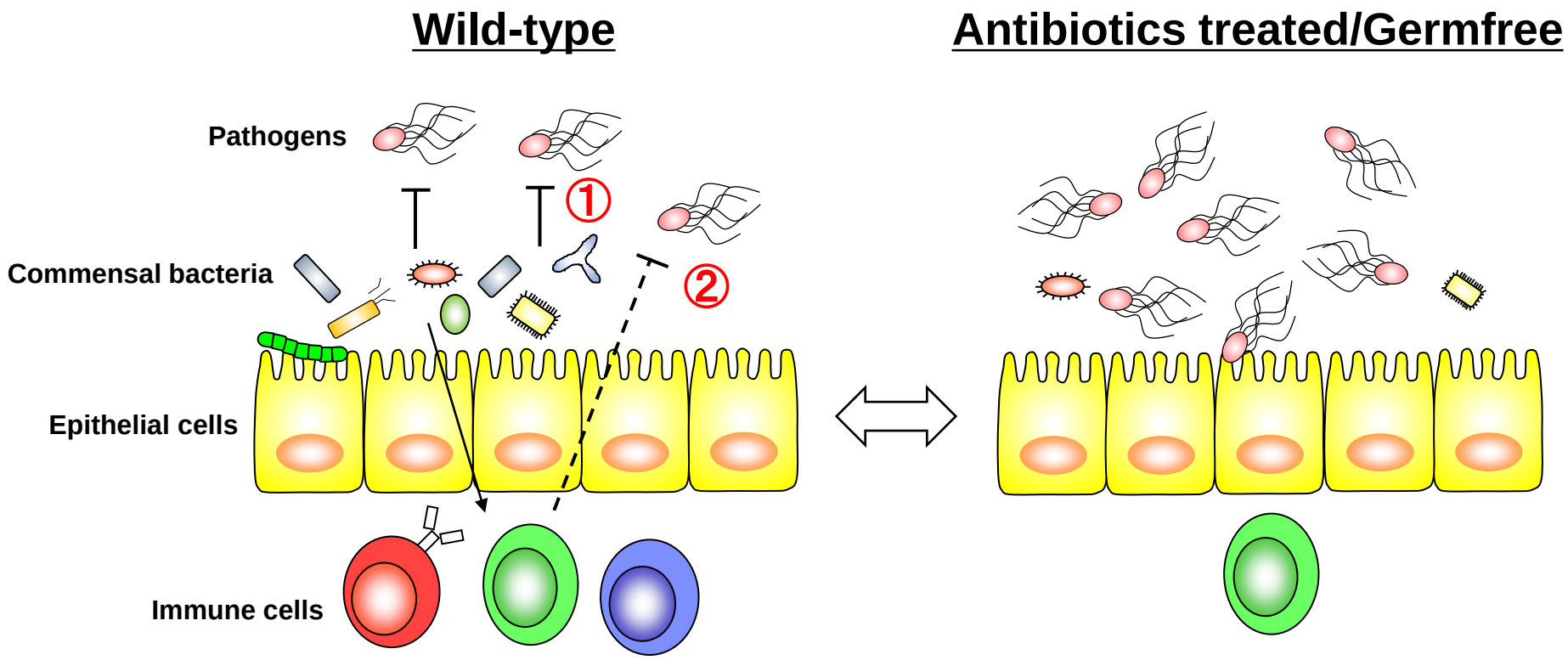
van Nood E, et al. *N Engl J Med*. 2013; 368: 407-415.



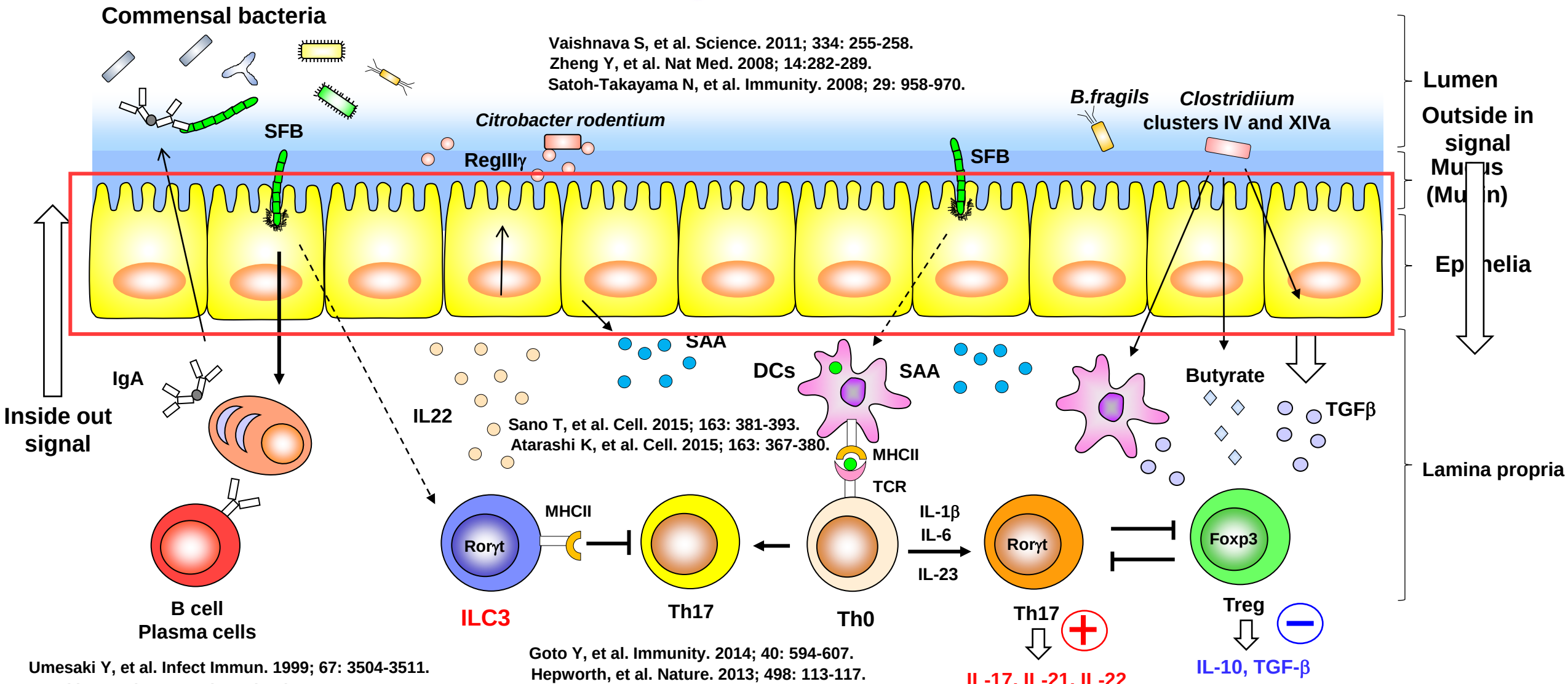
Chiba University hospital HP

Therapeutic approach based on “colonization resistance”

Commensal bacteria prevent intestinal pathogen infection



Intestinal homeostasis mediated by commensal bacteria and host immune cells

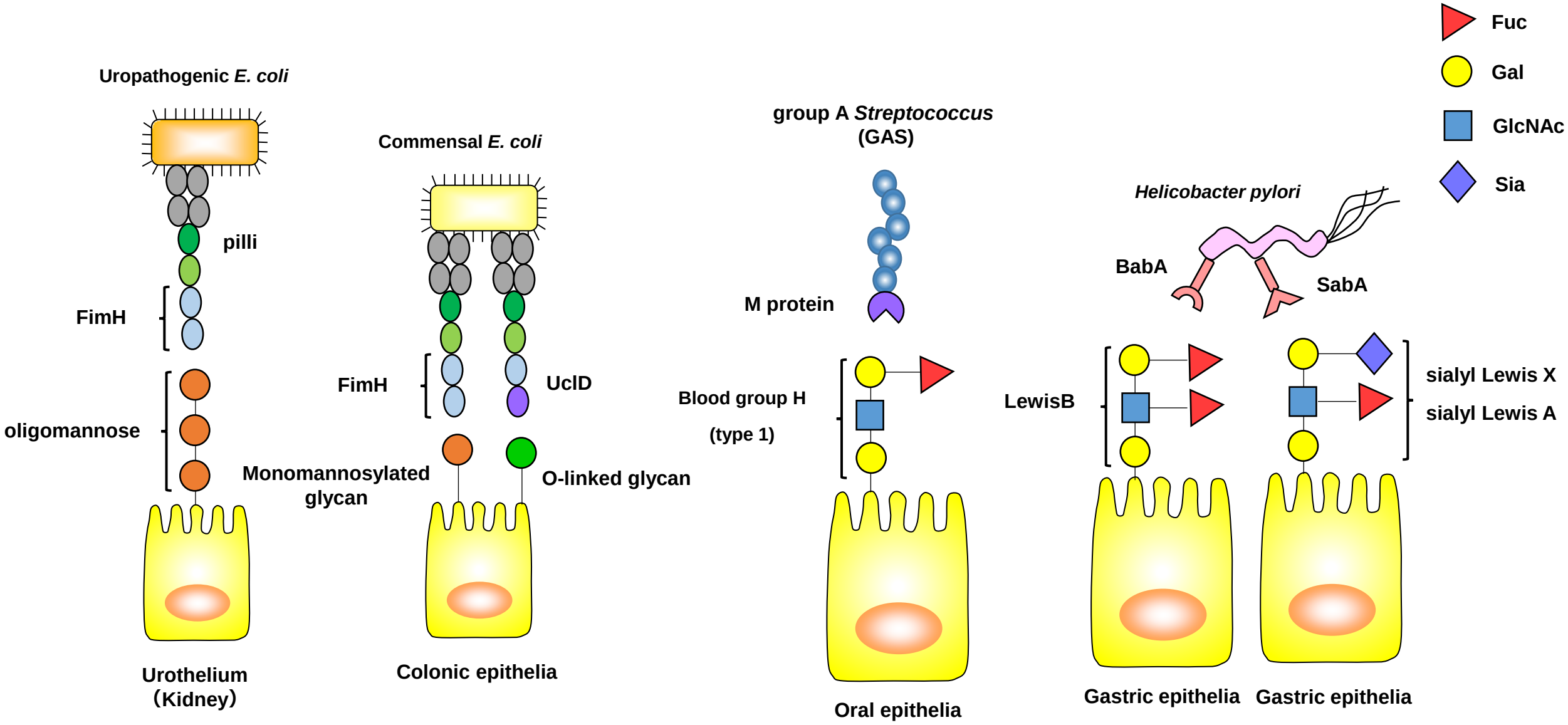


Today’s topics

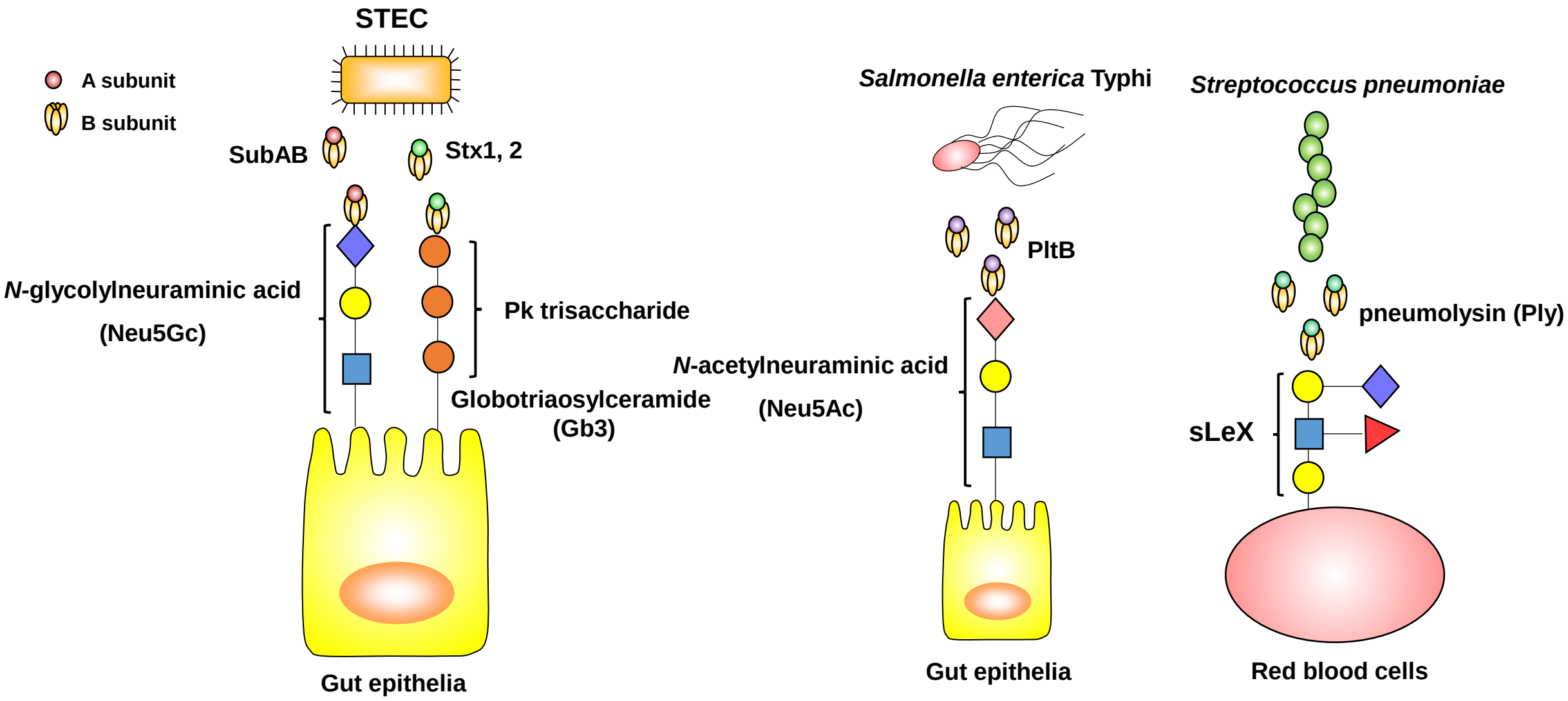
1. Interplay between commensal microorganisms and host immune system

2. Induction of intestinal epithelial glycosylation and phylaxis

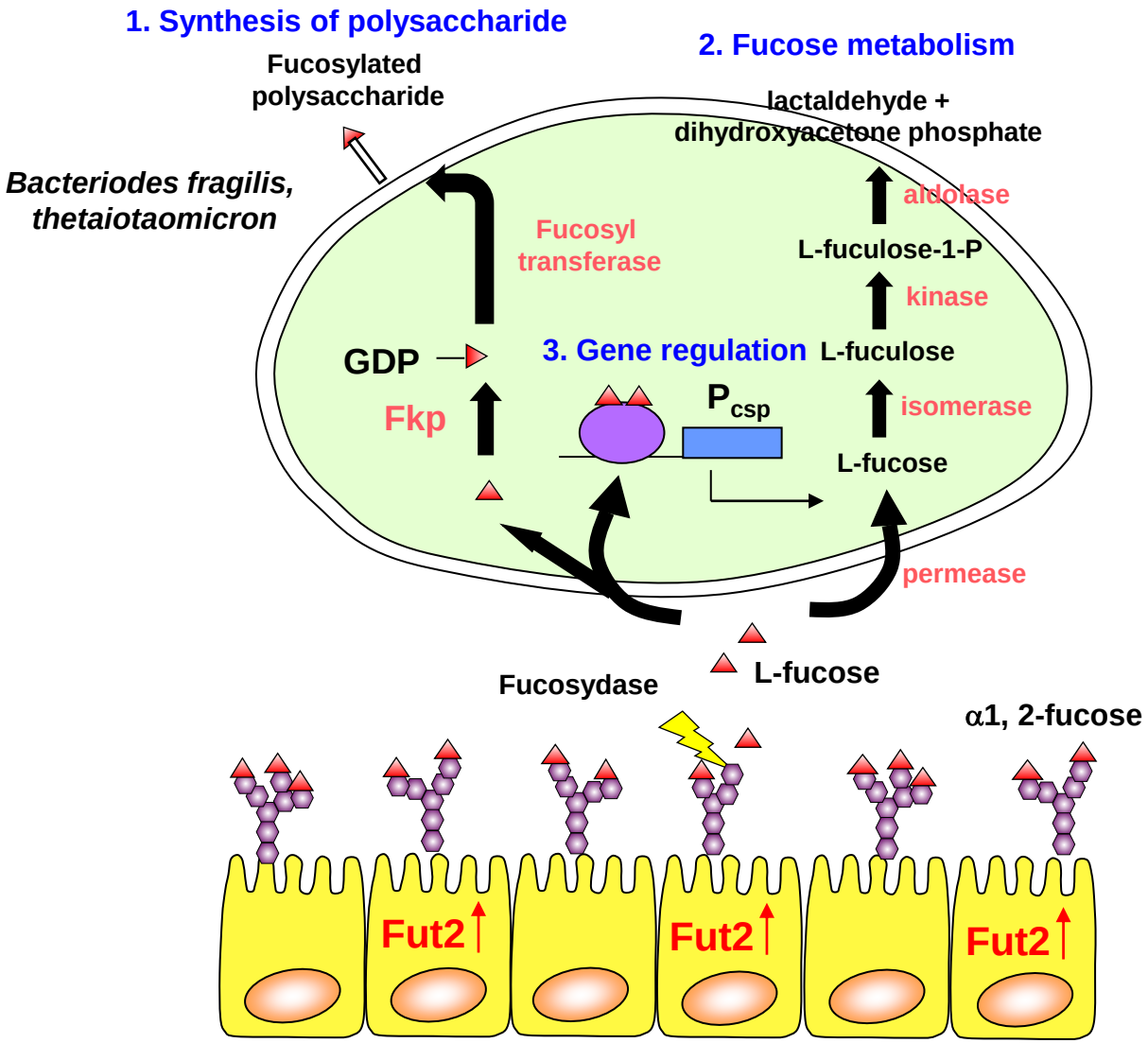
Pathogenic bacteria utilize epithelial carbohydrate chains (attachment)



Pathogenic bacteria utilize epithelial carbohydrate chains (toxin)

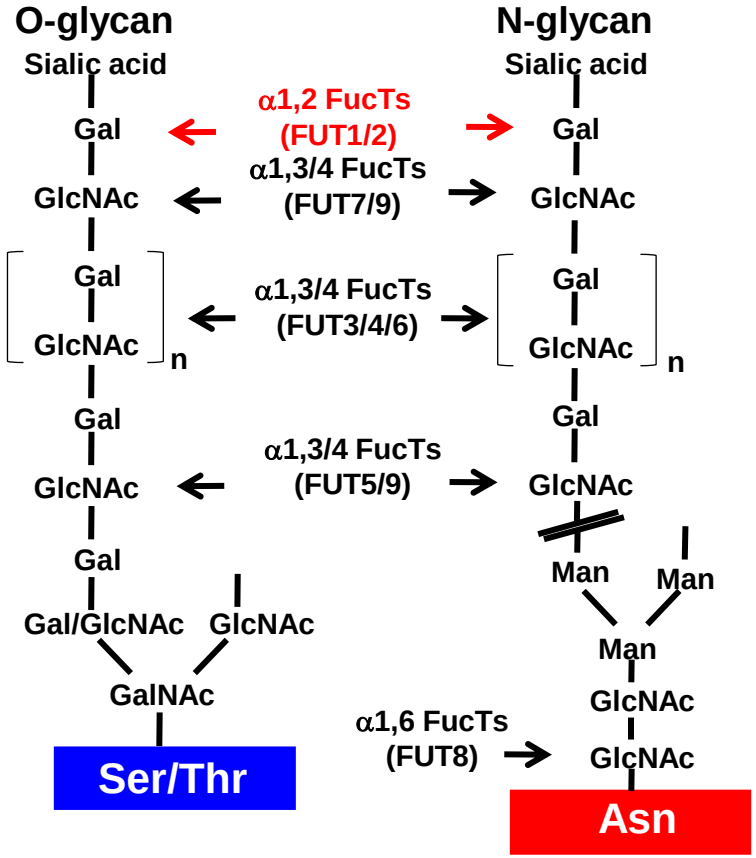


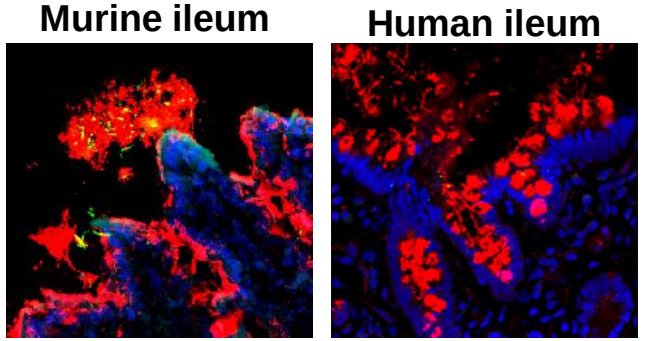
Intestinal epithelial α1,2-fucose is utilized by commensal bacteria



Bry L, *et al*. *Science*. 1996;273:1380-1383.
Hooper LV, *et al* . *PNAS*.1999;96:9833-9838.
Coyne MJ, *et al*. *Science*. 2005;307:1778-1781.
Comstock LE, Kasper DL. *Cell*. 2006 ;126:847-850.

Carbohydrate chain and fucosyltransferases





FUT2 non-sense polymorphism and human diseases

Human studies

FUT2 nonsense mutation 428G → A (Trp143→ stop)

Approximately 20 % of Europeans are homozygous recessive for the inactivating G428A mutation

Lindesmith L, *et al*. *Nat Med*. 2003;9:548-553

Human diseases

Adverse effects

1. FUT2 polymorphism (nonsense mutation) is associated with the incidence of type I diabetes

   Smyth DJ, *et al*. *Diabetes*. 2011;60:3081-3084

2. FUT2 polymorphism (nonsense mutation) is associated with the incidence of Crohn's disease

   McGovern DP, *et. al*. *Hum Mol Genet*. 2010;19:3468-3476. Franke A, *et al*. *Nat Genet*. 2010;42:1118-1125

3. FUT2 polymorphism (nonsense mutation) is associated with the incidence of primary sclerosing cholangitis

   Folseraas T, *et al*. *J Hepatol*. 2012;57:366-375

Beneficial effects

4. People with FUT2 polymorphism are resistant to the infection by Norwalk virus and rotavirus

   Lindesmith L, *et al*. *Nat Med*. 2003;9:548-553, Imbert-Marcille BM, *et al*. *J Infect Dis*. 2014;209:1227-1230

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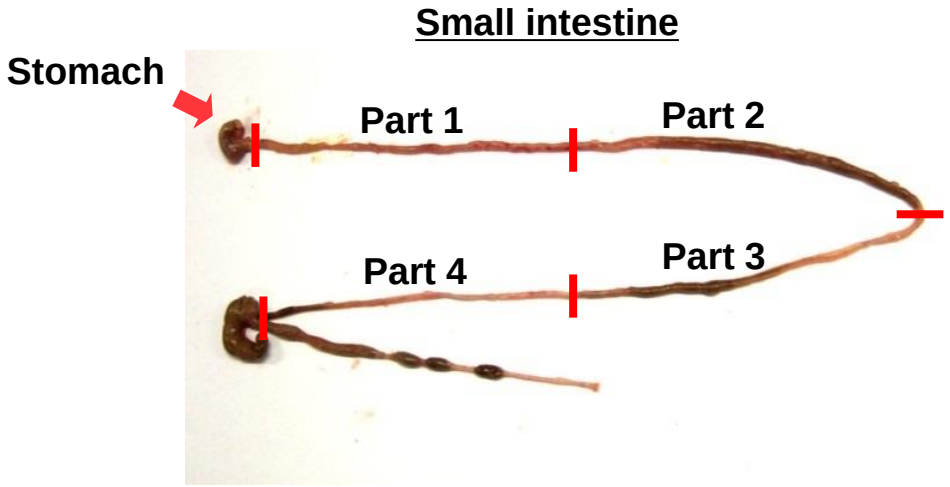
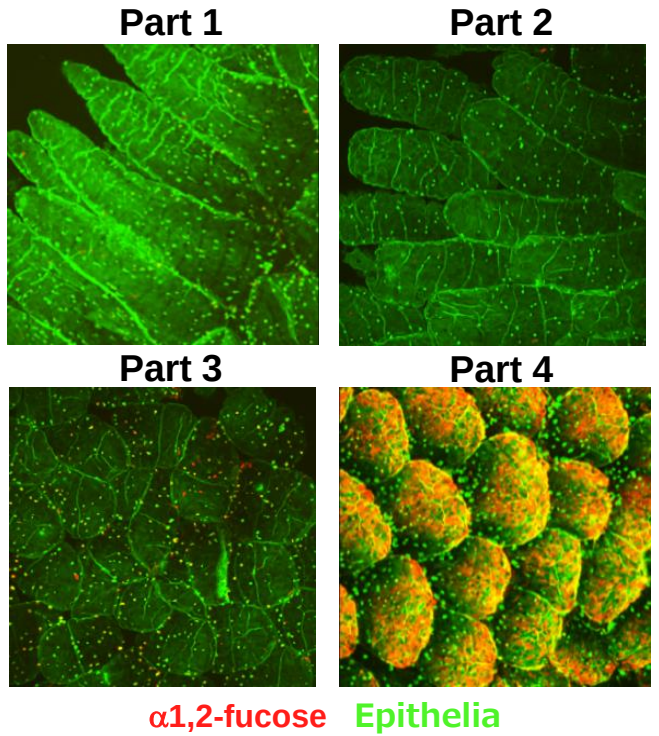
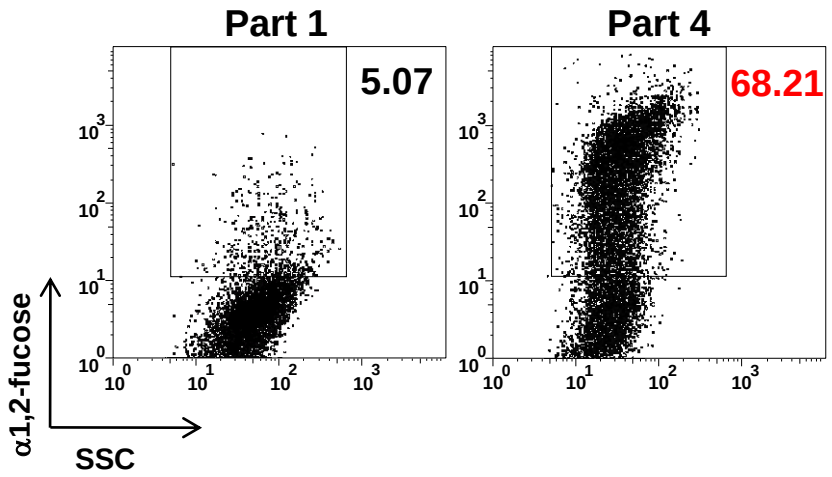
Biological trade-off system

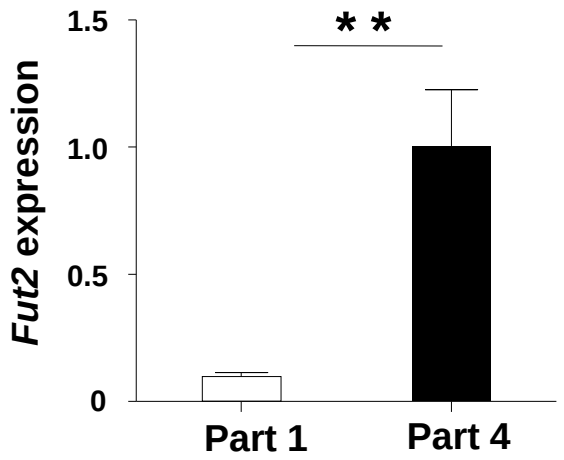
It is important to identify the mechanism of intestinal epithelial Fut2 and α1, 2-fucose medically and biologically

Ileal epithelial cells express Fut2 and α1,2-fucose

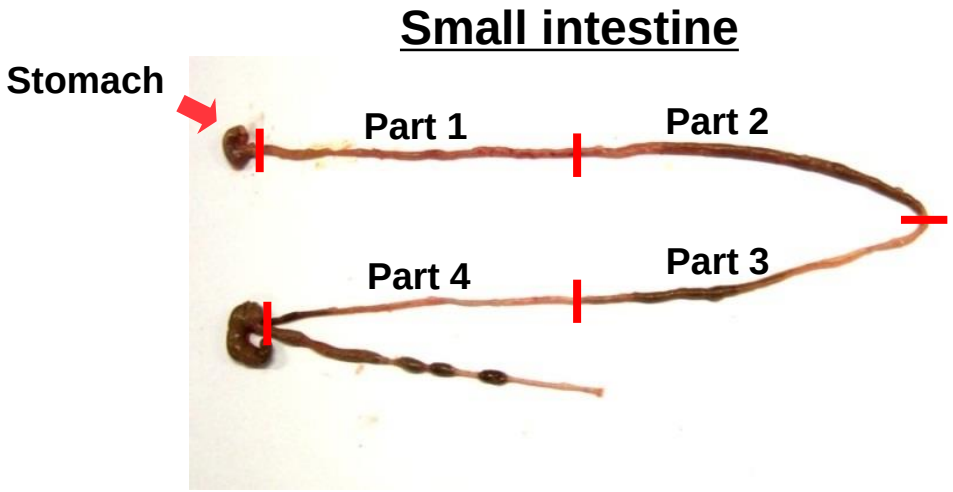


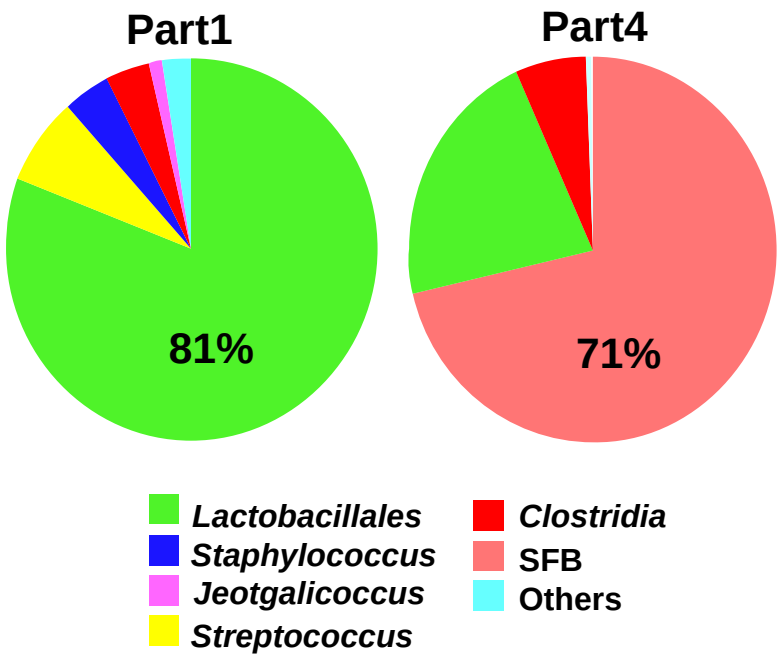


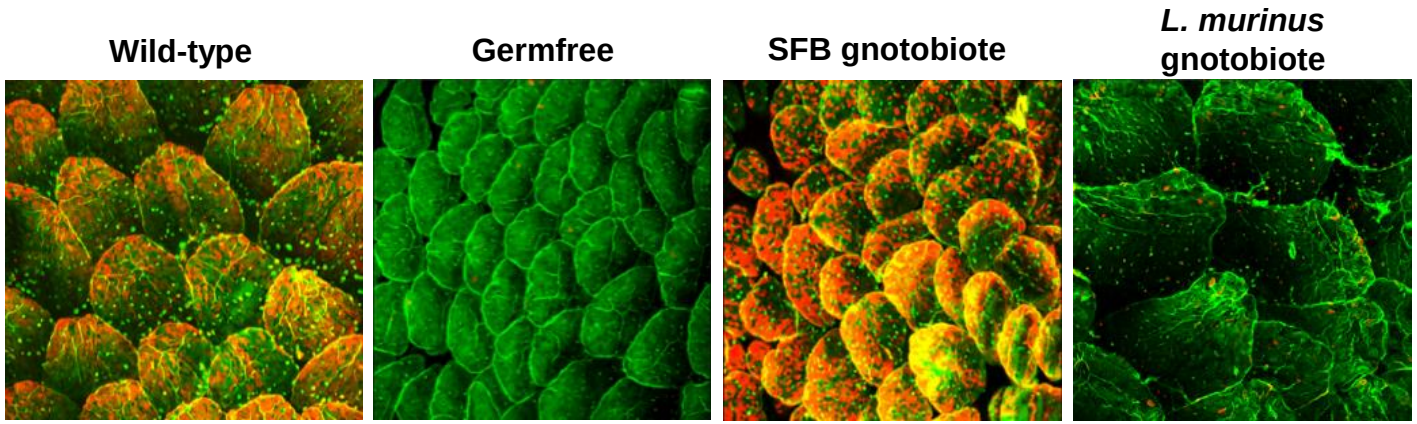


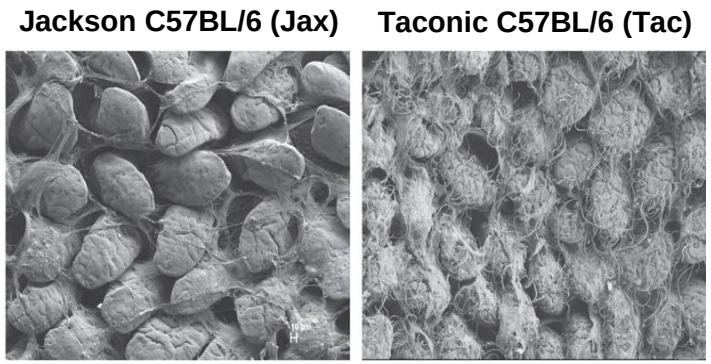


Segmented filamentous bacteria (SFB) induce α1, 2-fucose

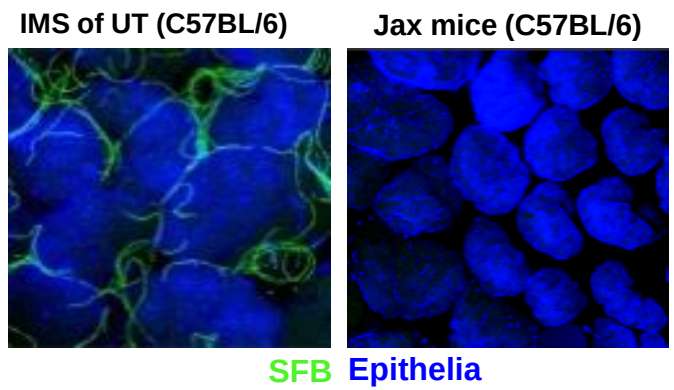


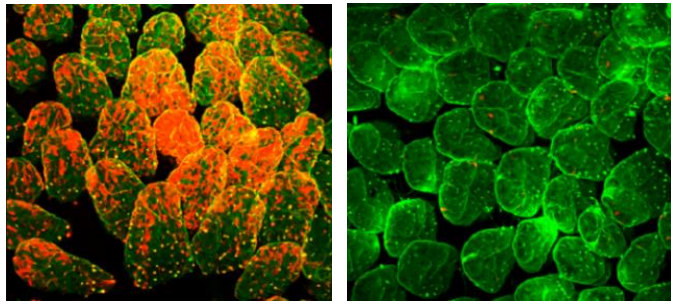




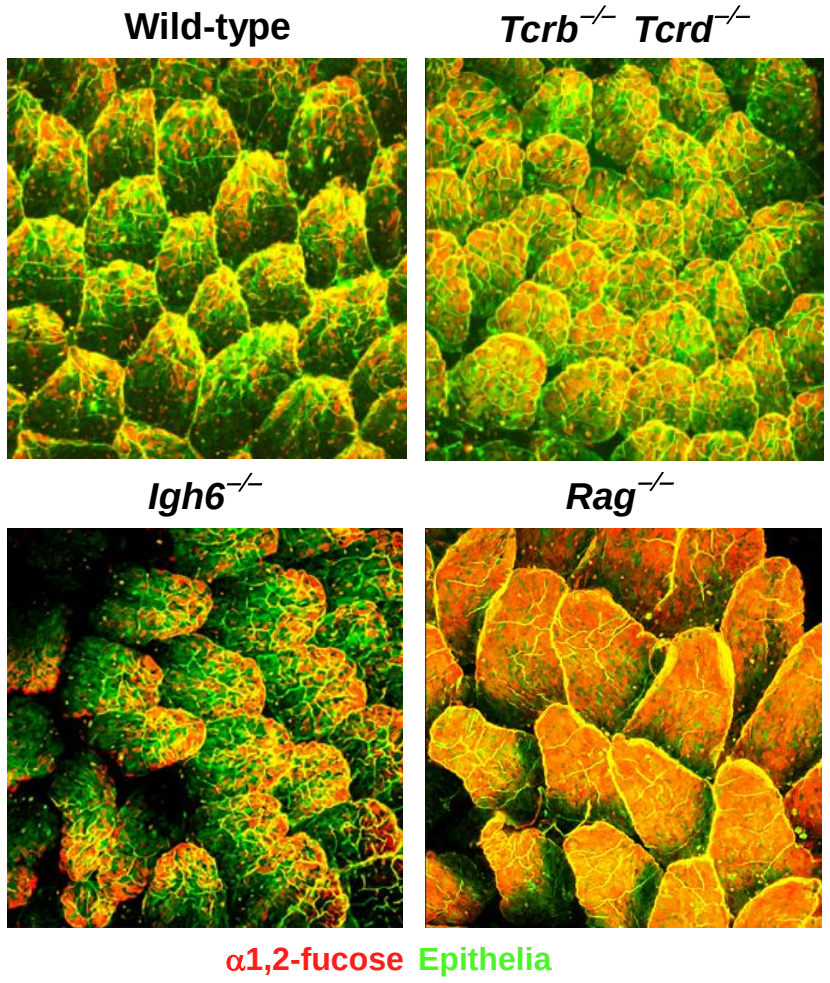


Ivanov I.I., *et al*. *Cell Host Microbe*. 2008;4:337-349.





B cells and T cells are not required for intestinal epithelial α1, 2-fucose

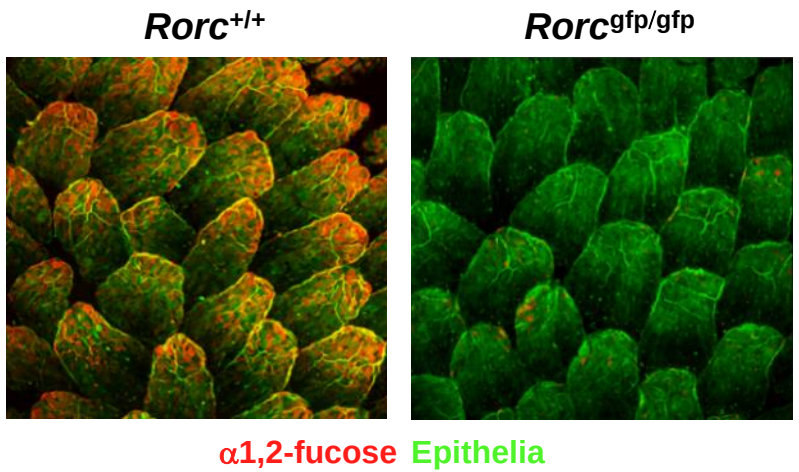


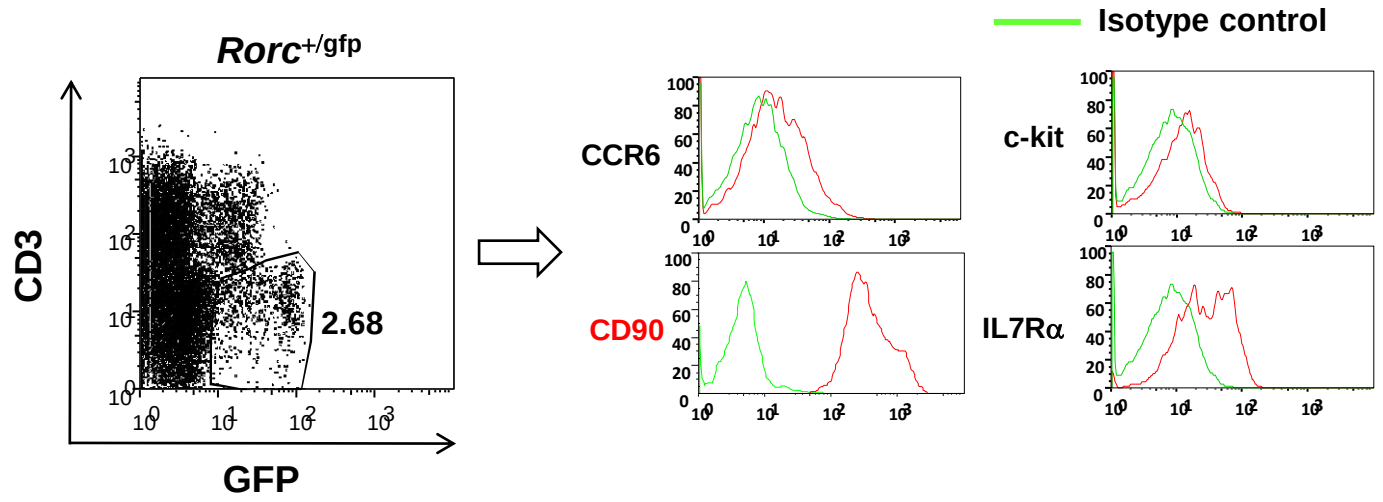
Tcrb$^{-/-}$ *Tcrd*$^{-/-}$ =T cell-deficient mcie

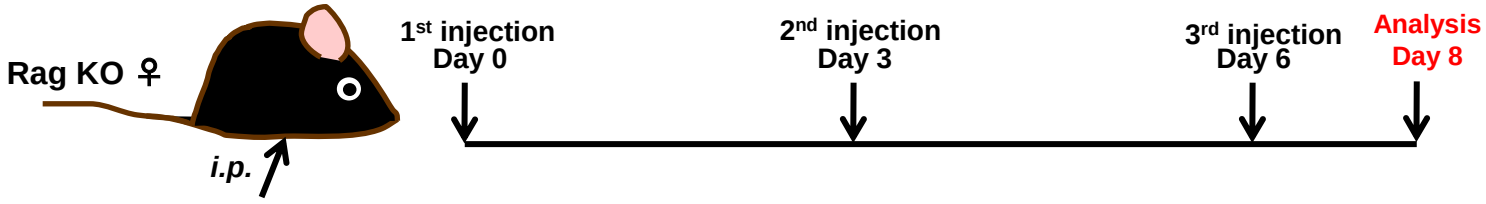
Igh6$^{-/-}$=B cell-deficient mice

Rag$^{-/-}$=T and B cell-deficient mice

Group 3 innate lymphoid cells (ILC3) are required for intestinal epithelial α1, 2-fucose

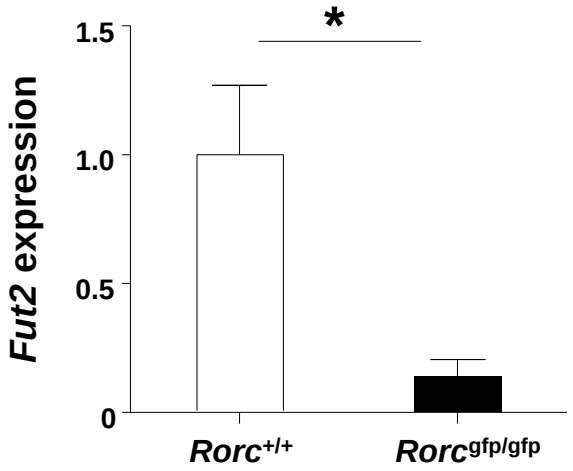


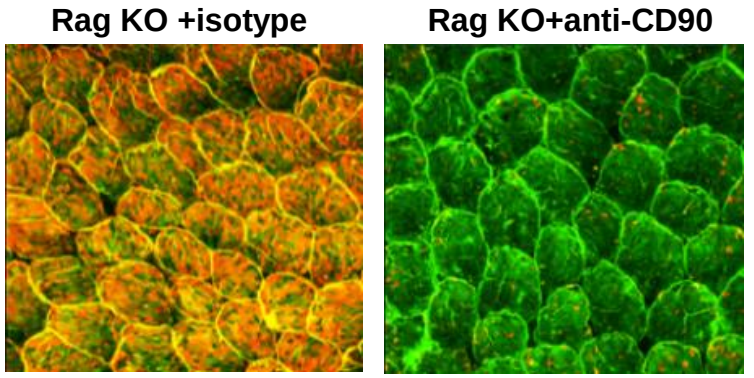


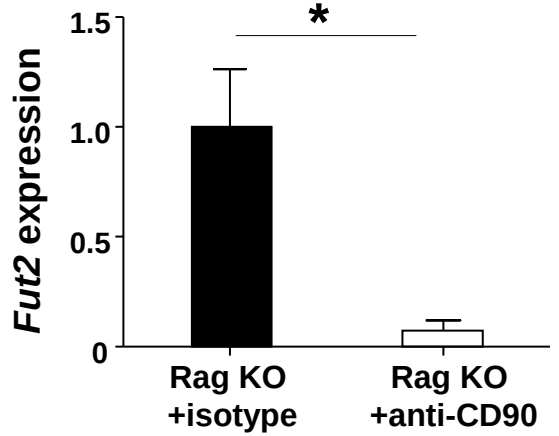


anti-CD90 or isotype control Ab (250 μg/mouse)

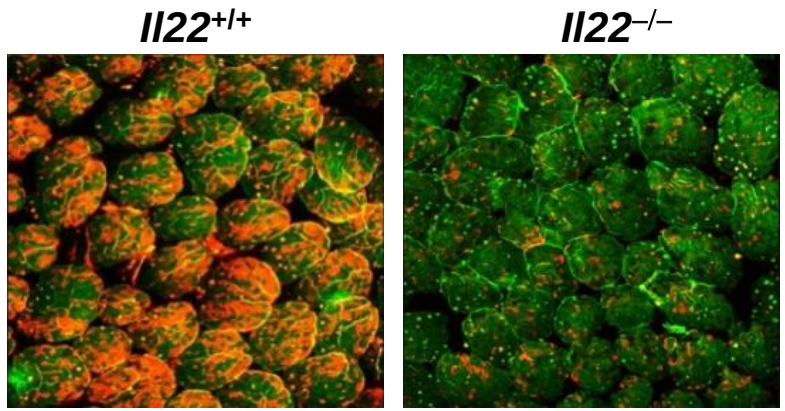
Sonnenberg GF, *et al*. *Immunity*. 2011 ;34:122-134

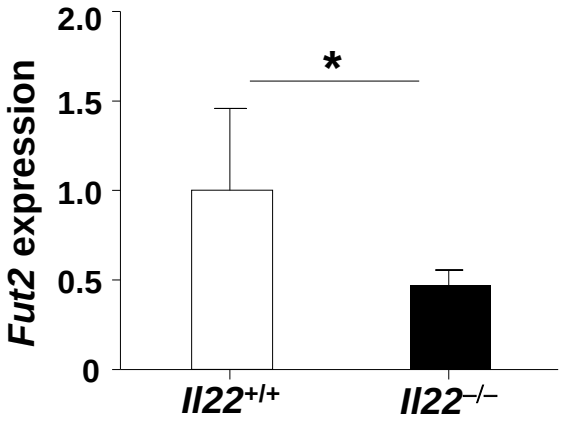


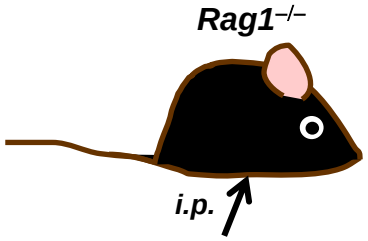




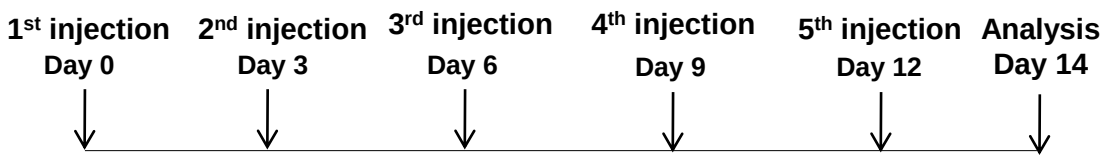
IL-22 produced from ILC3 is required for the induction of epithelial α1, 2-fucose

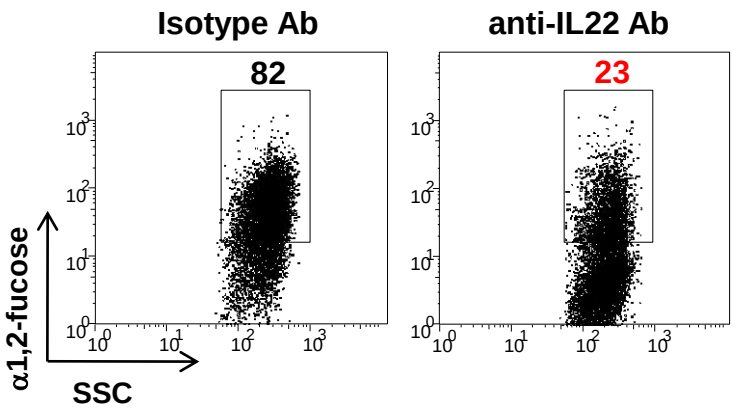


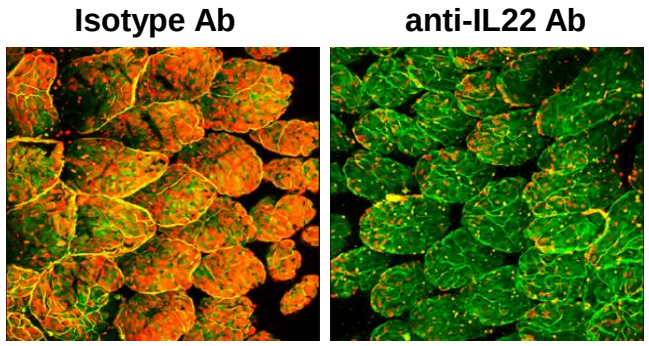


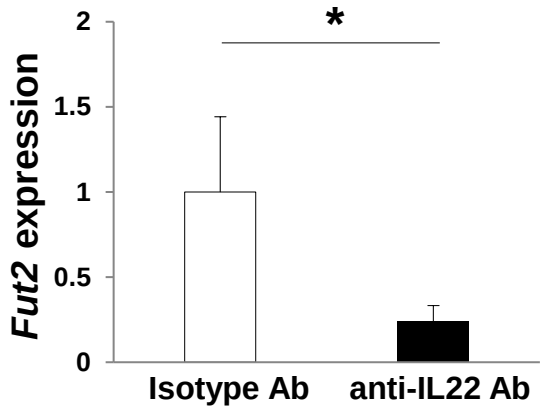


anti-IL22 or isotype Ab
(250 μg/mouse)

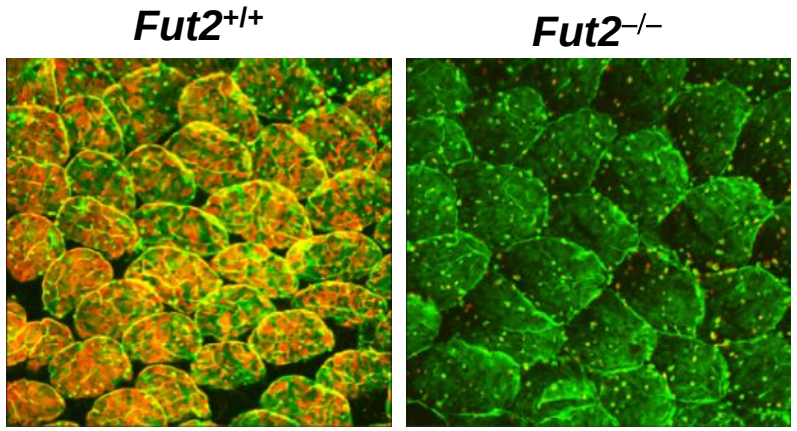


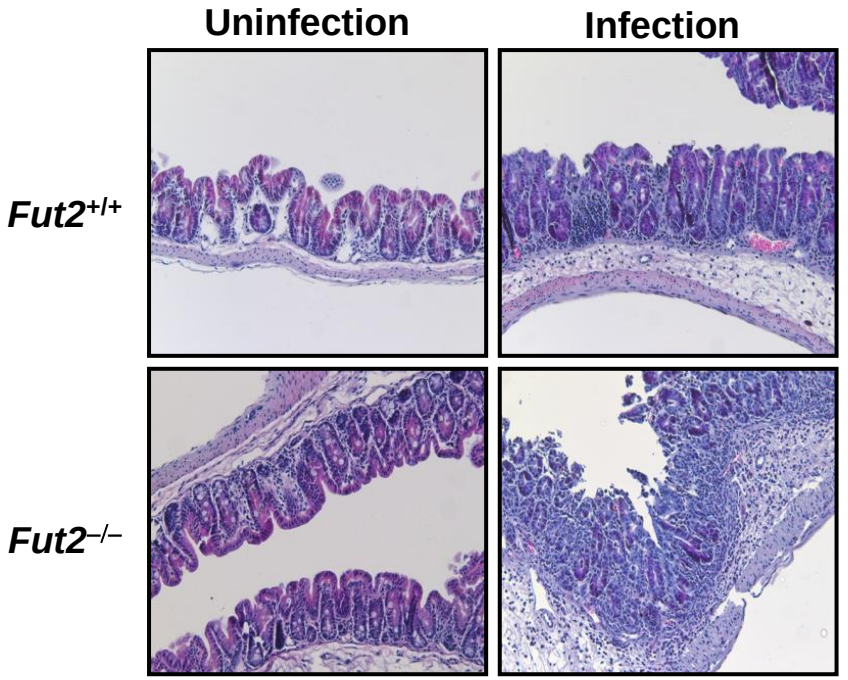


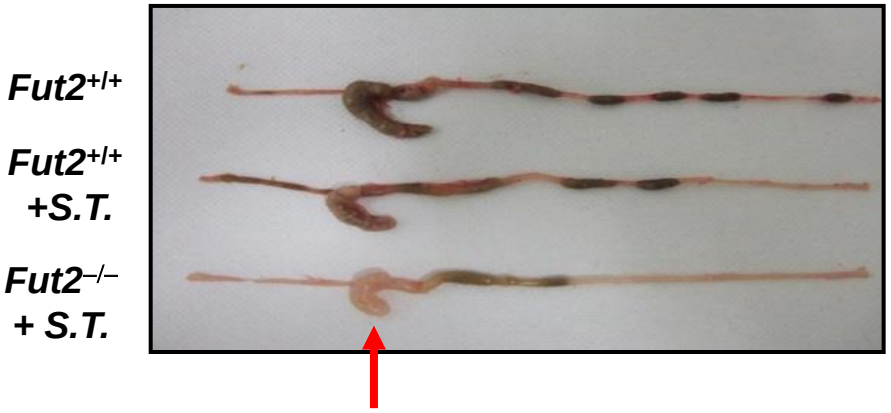


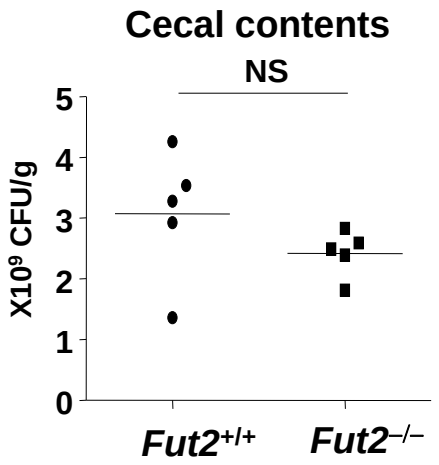


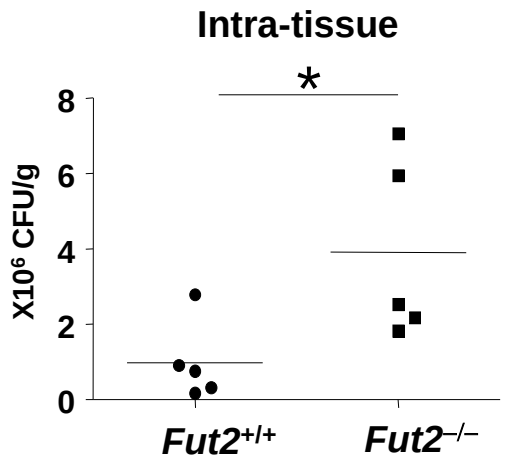
Fut2-deficient mice are resistant to the infection by *Salmonella typhimurium*



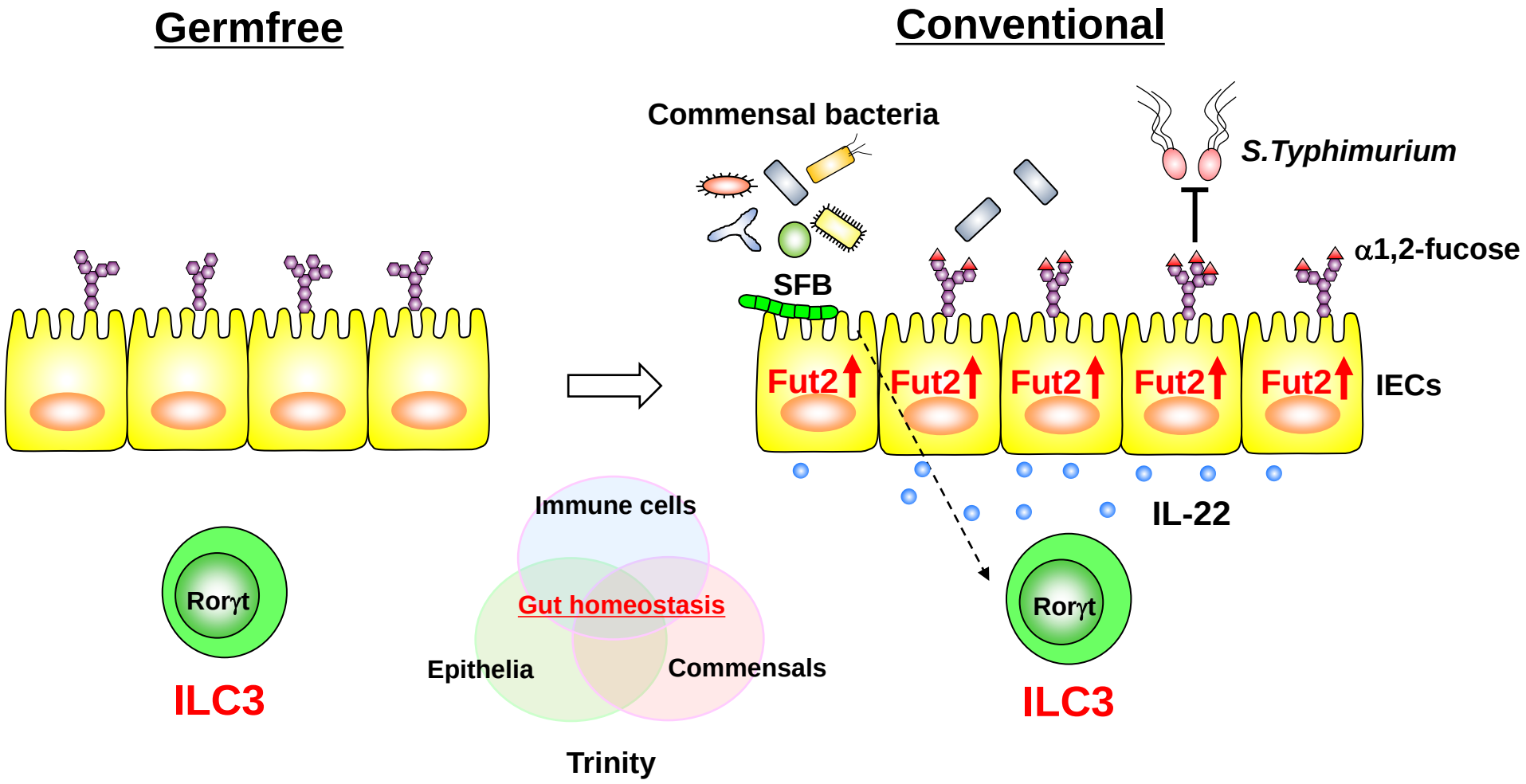








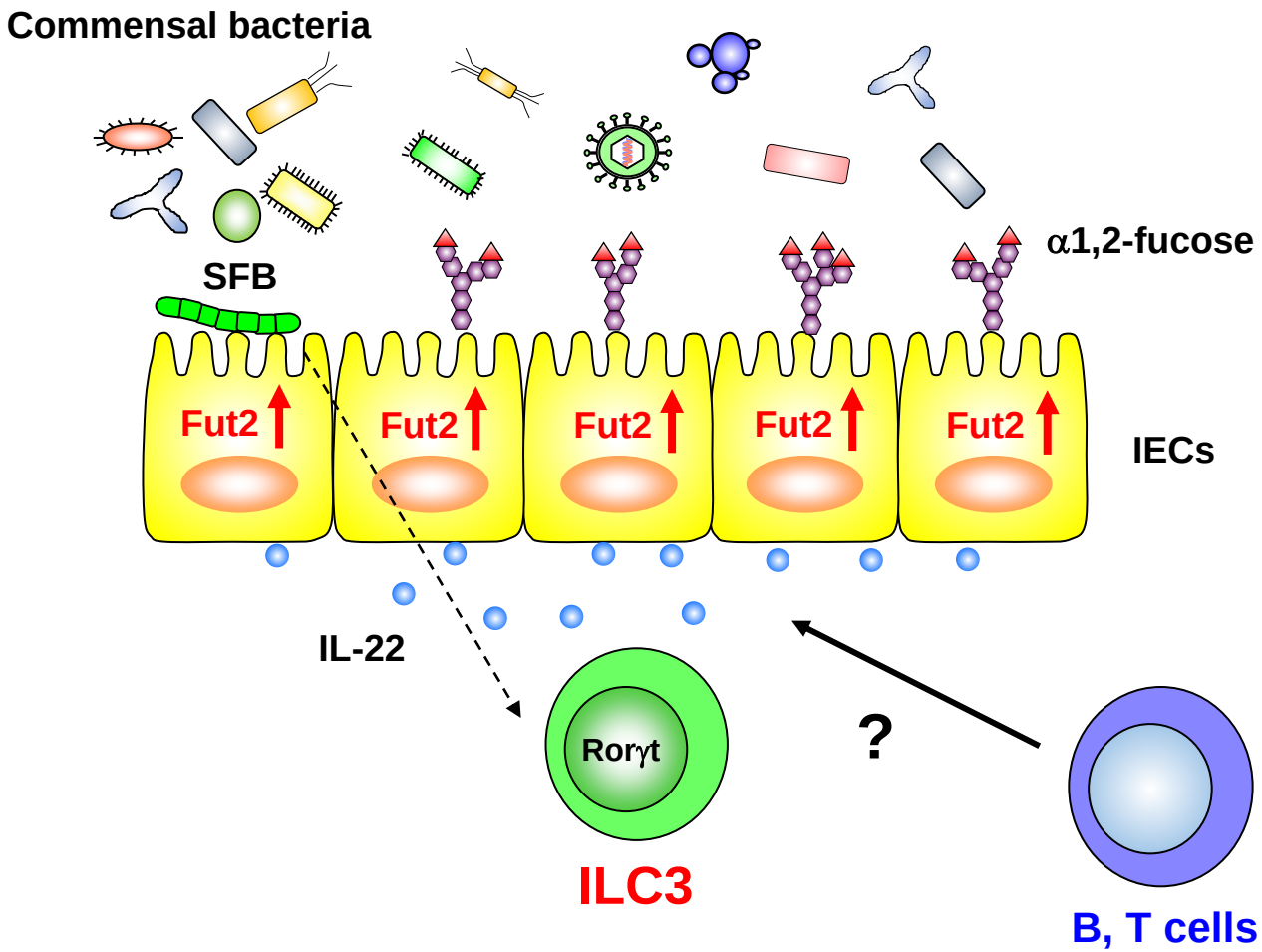
Scheme of intestinal epithelial α1, 2-fucosylation



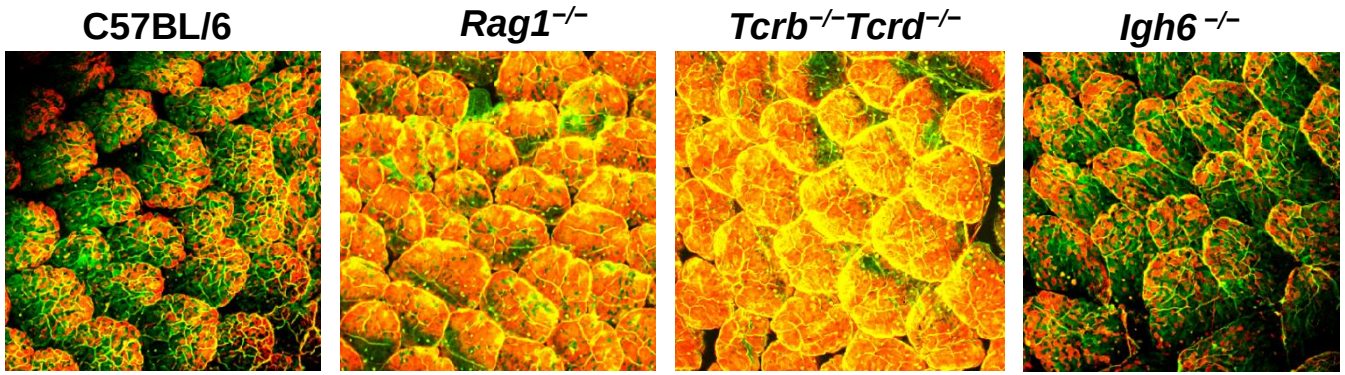
Goto Y, *et al*. *Science*. 345: 1254009, 2014

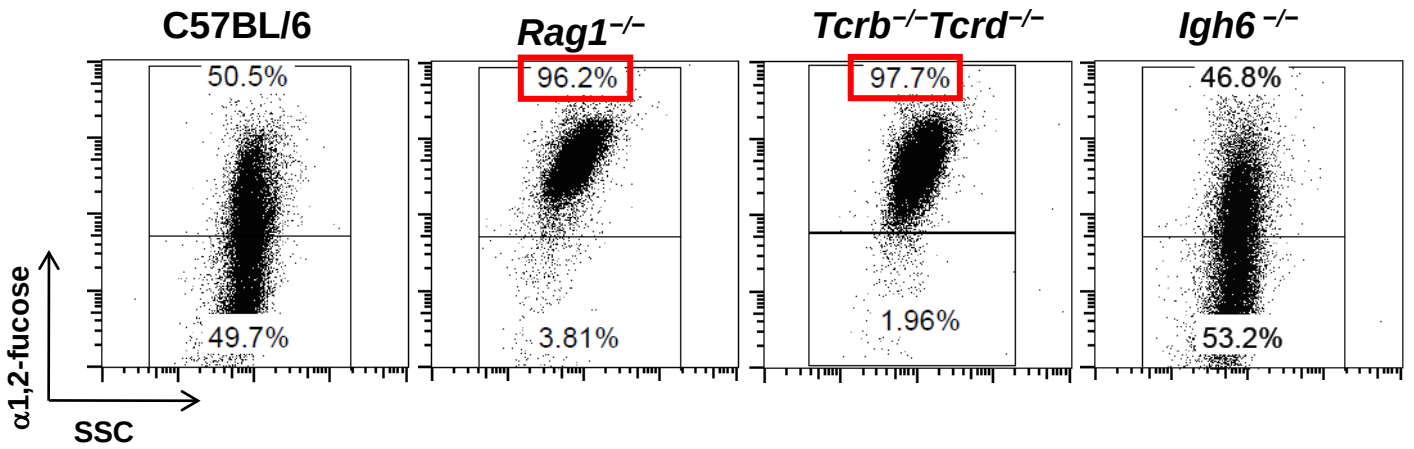
There is a possibility that intestinal epithelial glycosylation is regulated and modulate bacterial infection

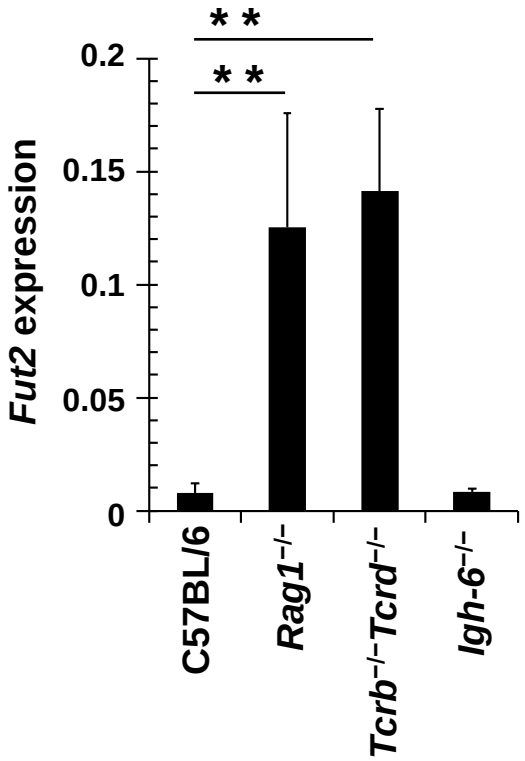
How about the role of acquired immune cells in the regulation of epithelial α1, 2-fucose?



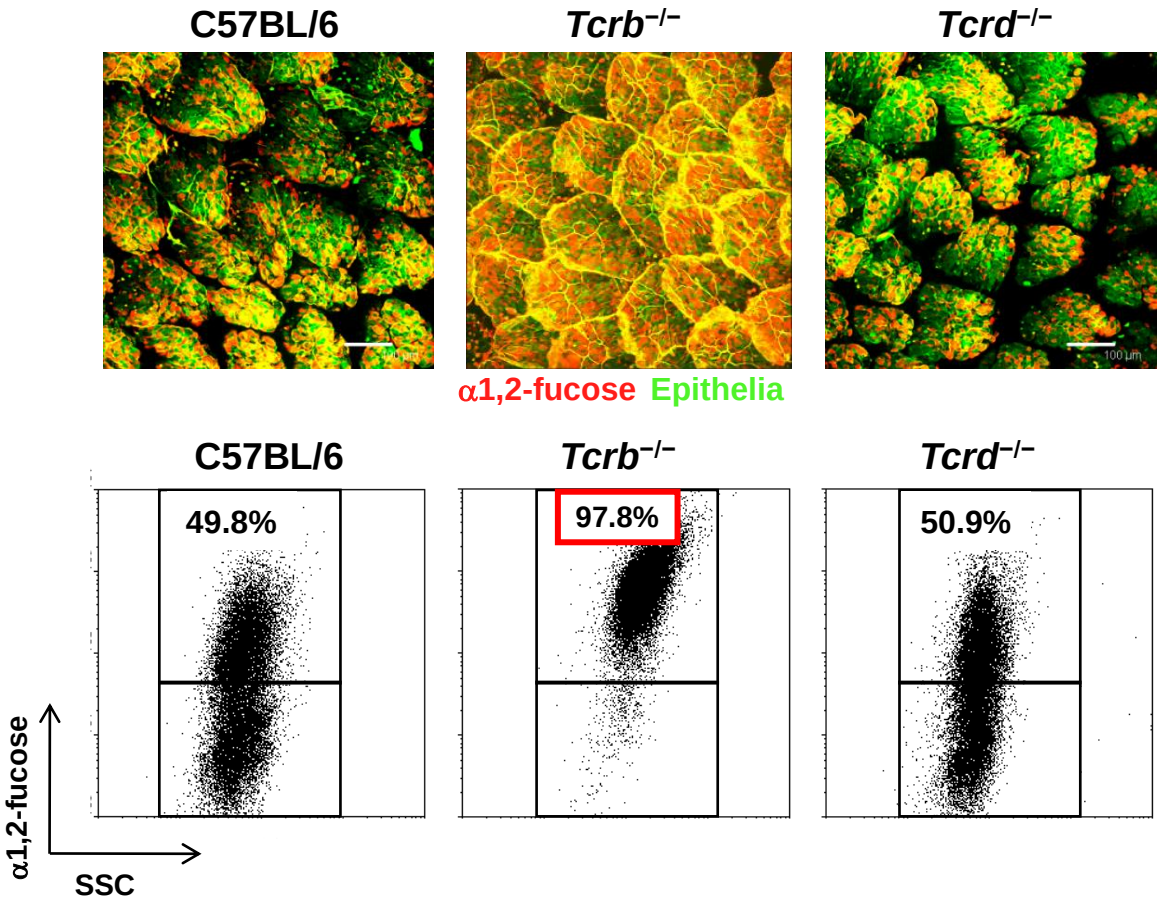
T cells inhibit α1, 2-fucosylation

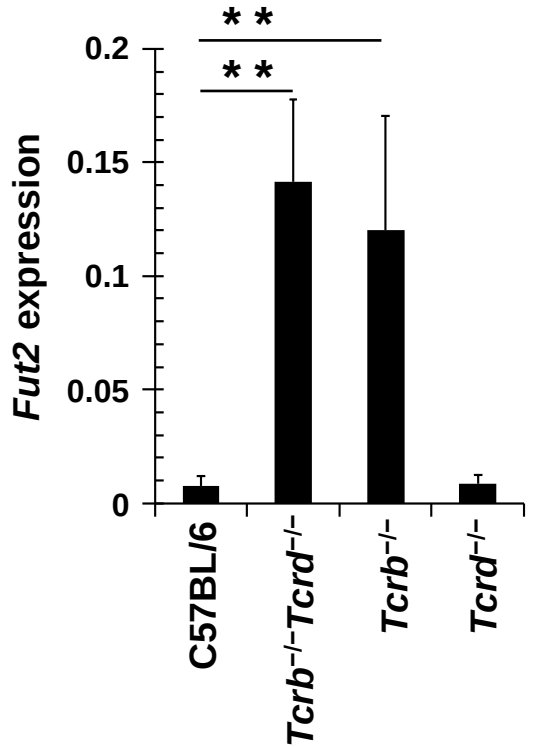




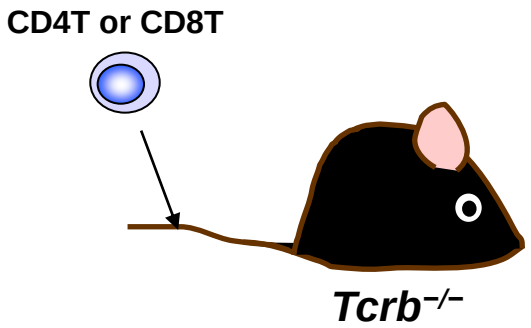


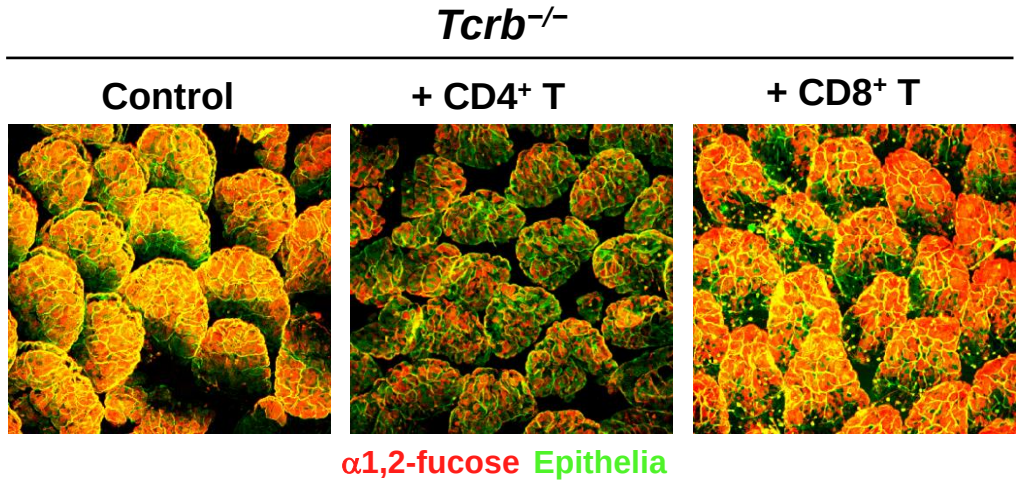
TCR αβ+ T cells inhibit α1, 2-fucosylation

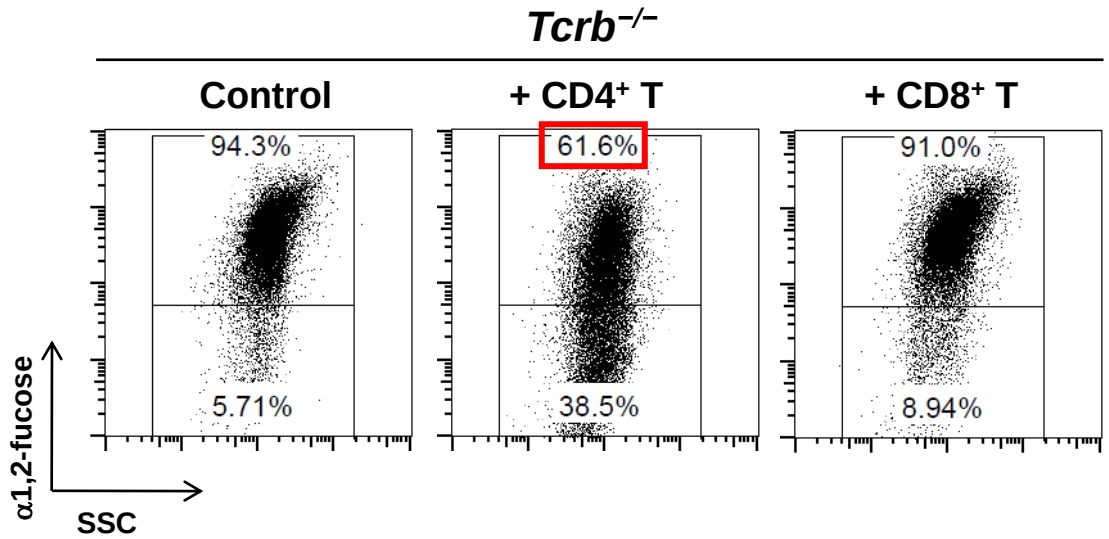


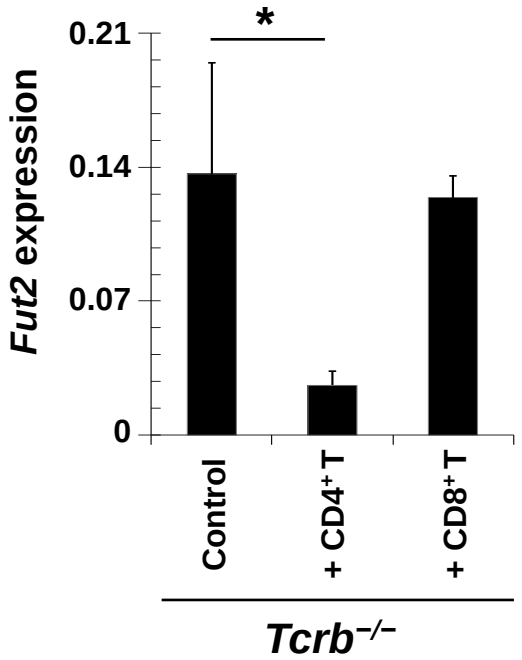


TCR αβ⁺ CD4⁺ T cells inhibit epithelial α1, 2-fucosylation

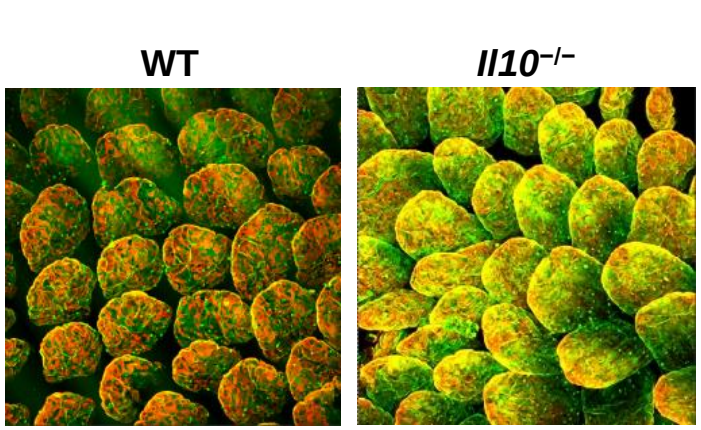


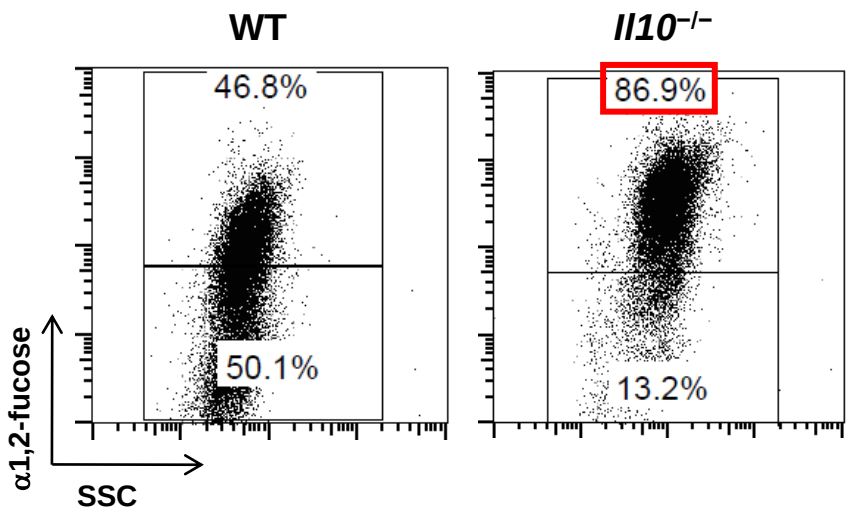


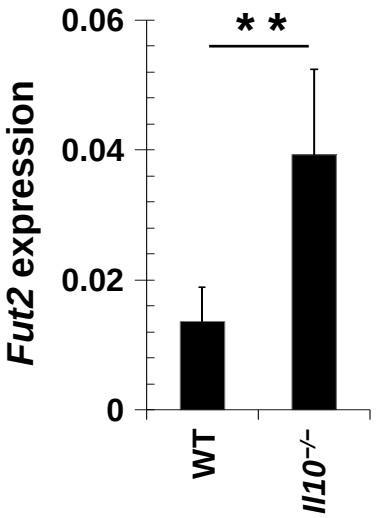


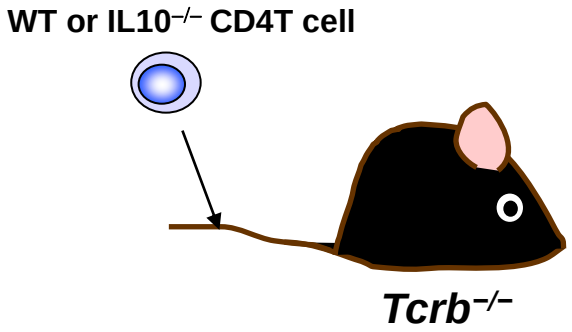


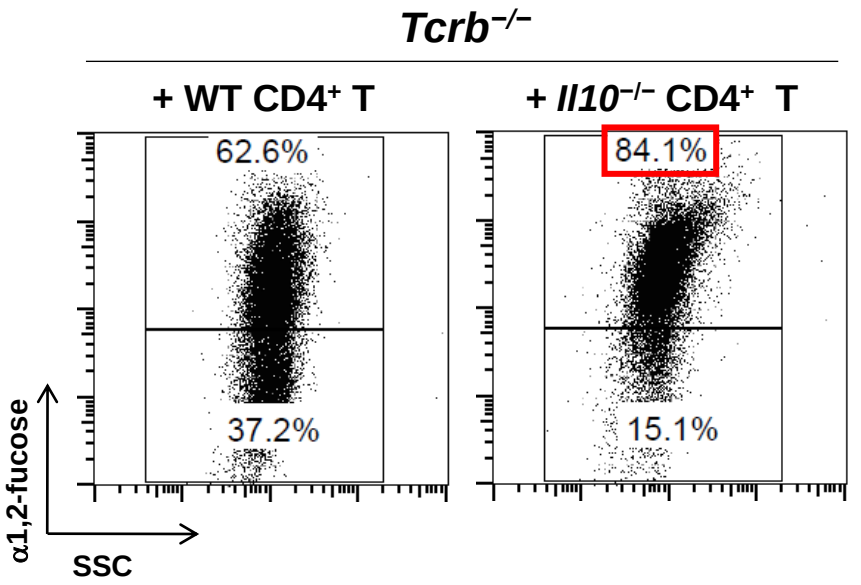
IL-10 produced from CD4 T cells inhibit epithelial α1, 2-fucose

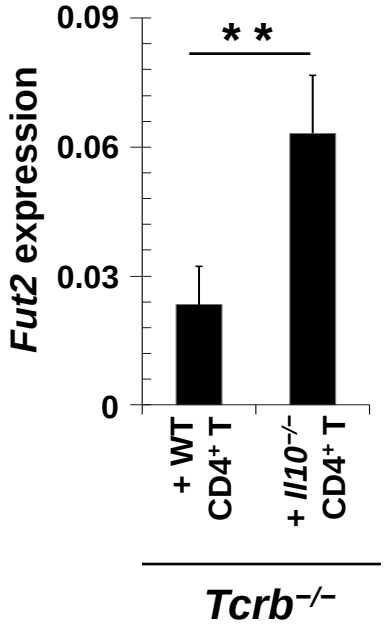




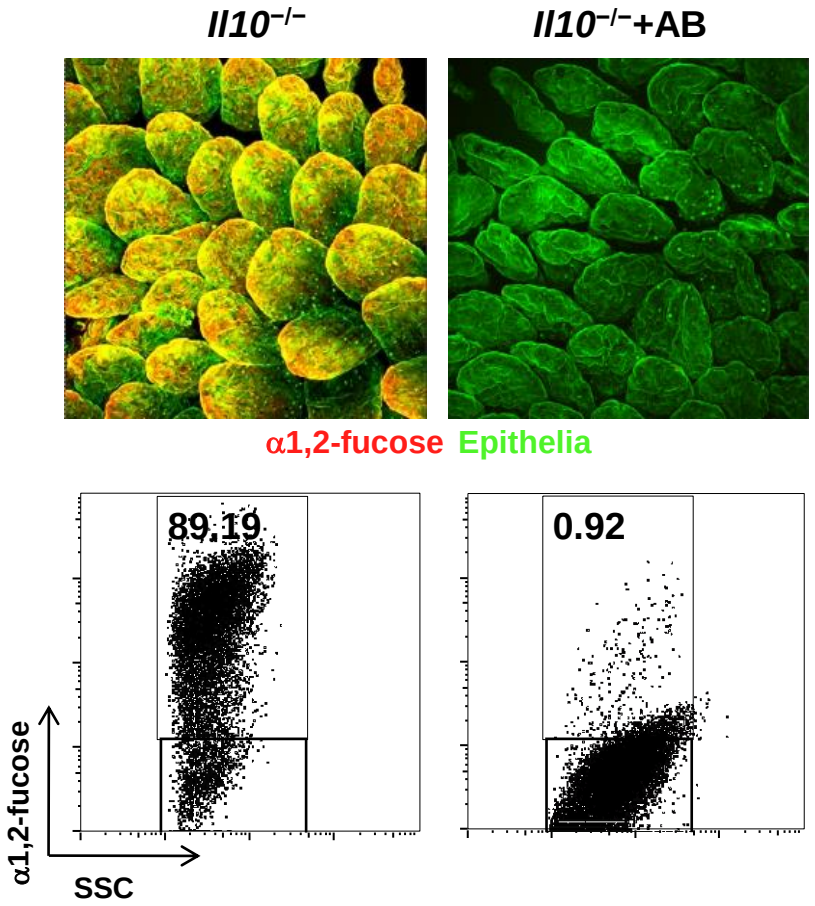




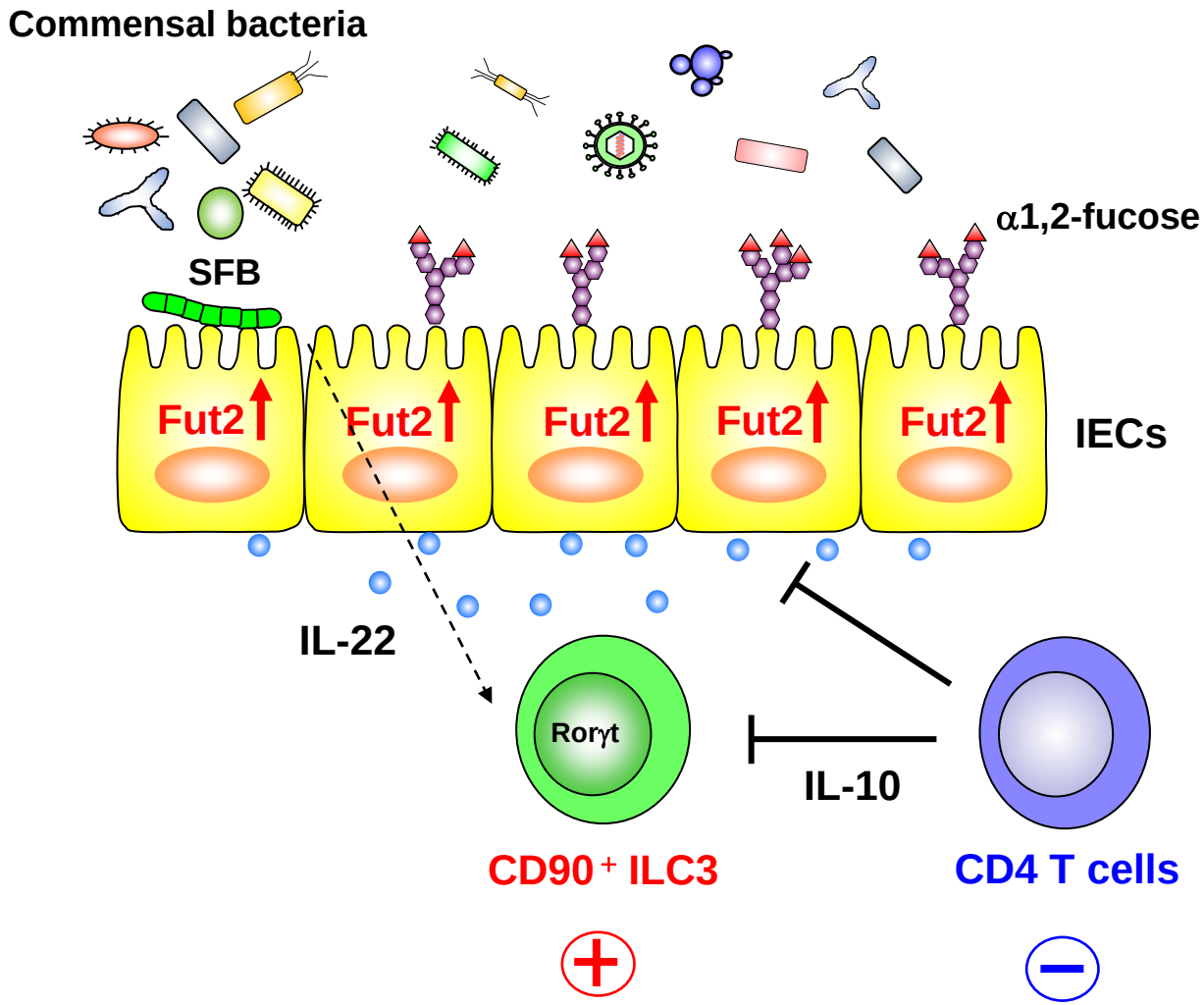




α1, 2-fucosylation in IL-10-deficient mice are dependent on commensal bacteria



Epithelial α1, 2-fucosylation is regulated by innate and acquired immune cells

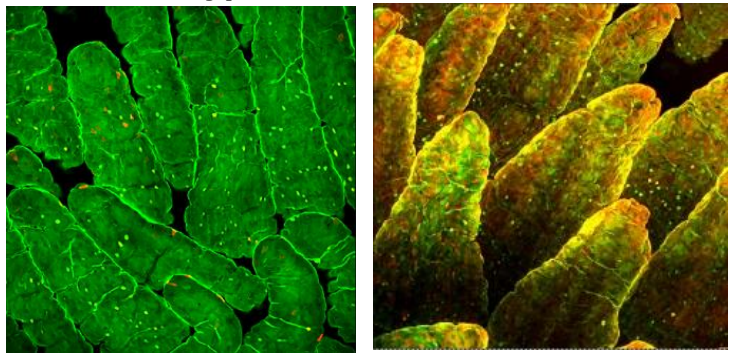


Goto Y, et al. *Sci Rep*. 5: 15918, 2015

Inflammation enhance the epithelial α1,2-fucosylation

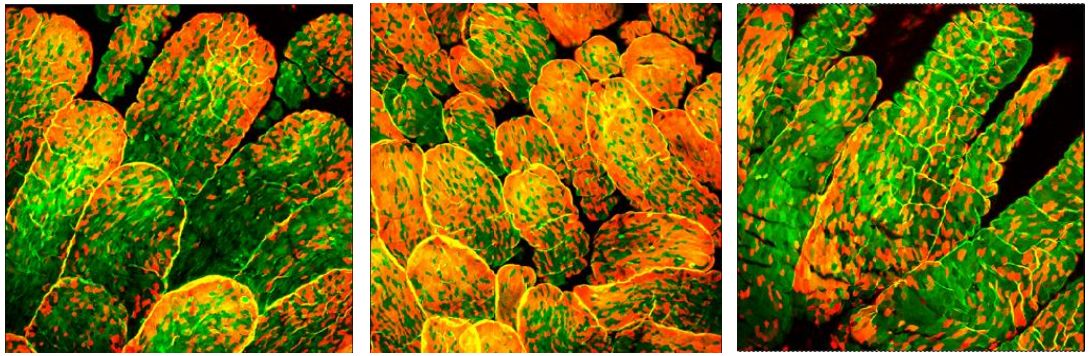
Chronic inflammation

Wild-type | *Il10* $^{-/-}$



Acute inflammation

5% DSS treat | NSAID treat | 9 Gy irradiation



α1,2-fucose Epithelia

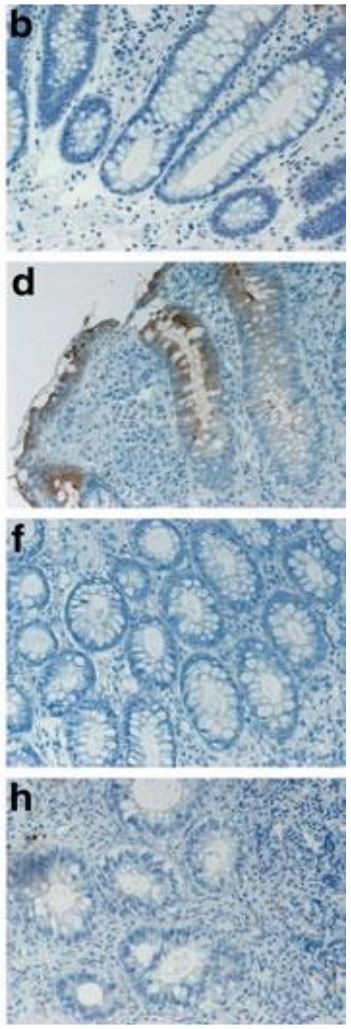
Human tissue

Healthy people

Colonic CD

Ileocolonic CD

UC



α1,2-fucose

Miyoshi J, et al. *J Gastroenterol*. 2011; 46: 1056-1063.

There is a possibility that intestinal epithelial glycosylation is utilized as a marker of inflammation