Norovirus and gut microbiota: friend or foe?

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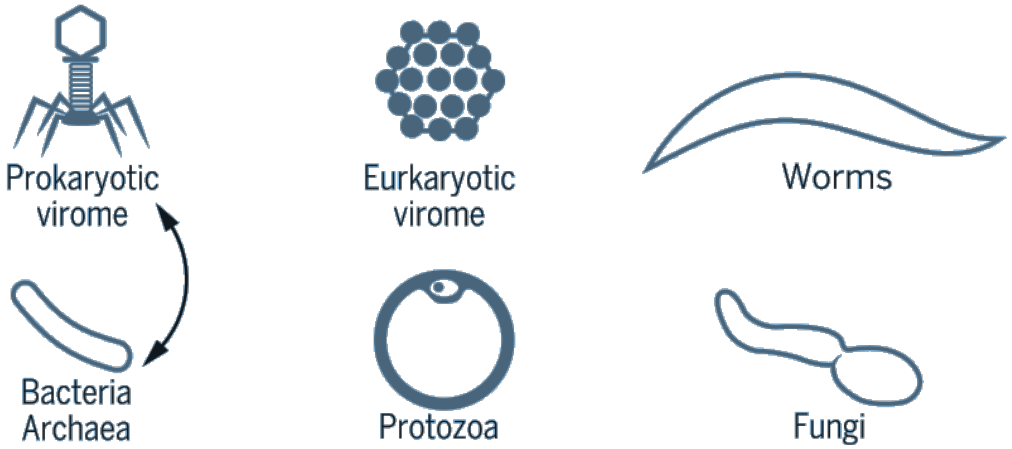
Gut microbiota

- # gut microbes ~ 10^{14}
- roughly 10 times > human cells

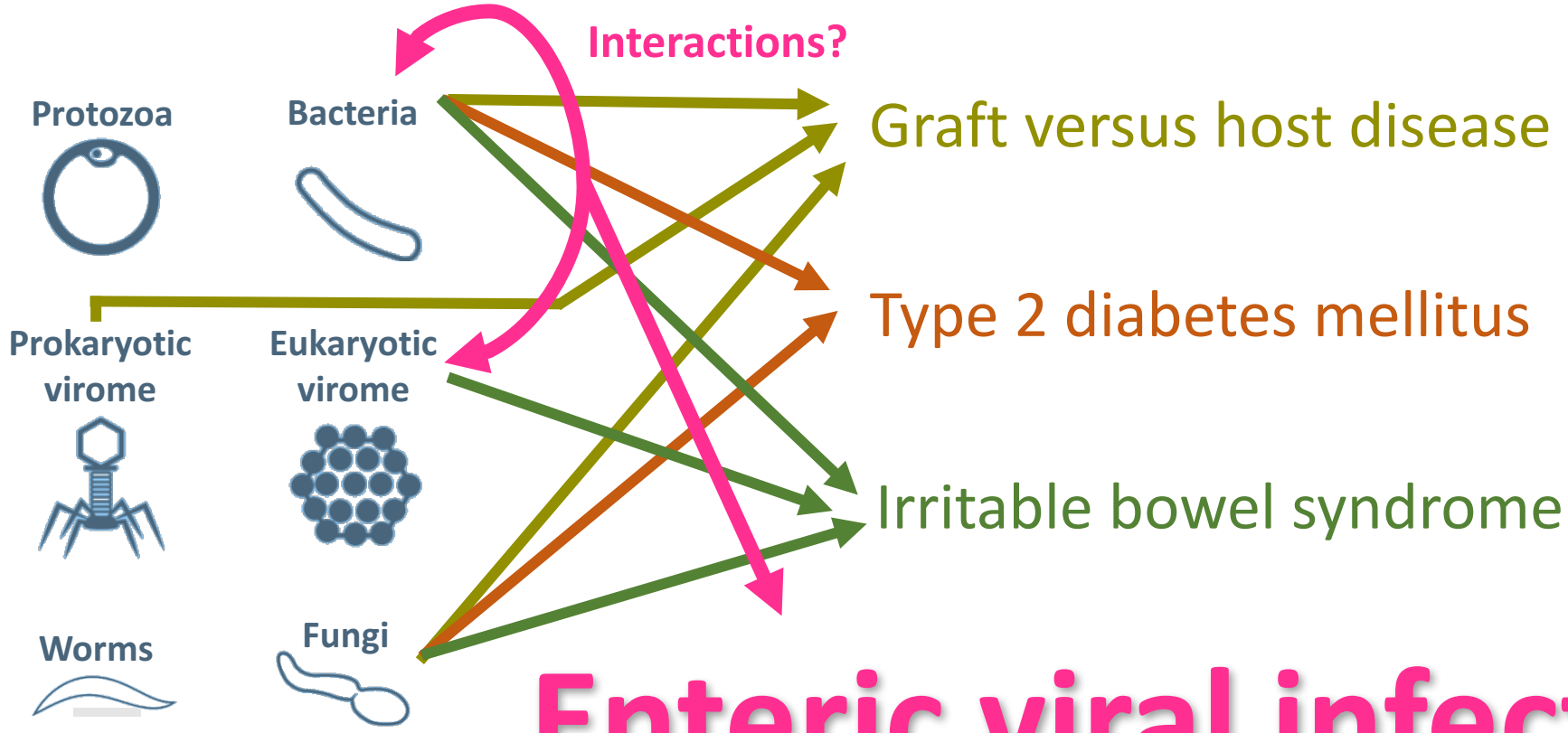


Functions

- Modulates our immune responses
- Regulates our gut motility
- Degrades indigestible dietary substances → energy source

(Thursby E et al., Biochemical Journal, 2017;Pfeiffer JK et al., Science, 2016; Karst SM, Nature Reviews Microbiology, 2016)

Gut microbiota X diseases



Enteric viral infections

Second most common infections after respiratory viral infections

(Thursby E et al., Biochemical Journal, 2017;Pfeiffer JK et al., Science, 2016; Karst SM, Nature Reviews Microbiology, 2016)

Norovirus:

today example to illustrate enteric virus-gut microbiota interactions

Norovirus: the most common enteric virus

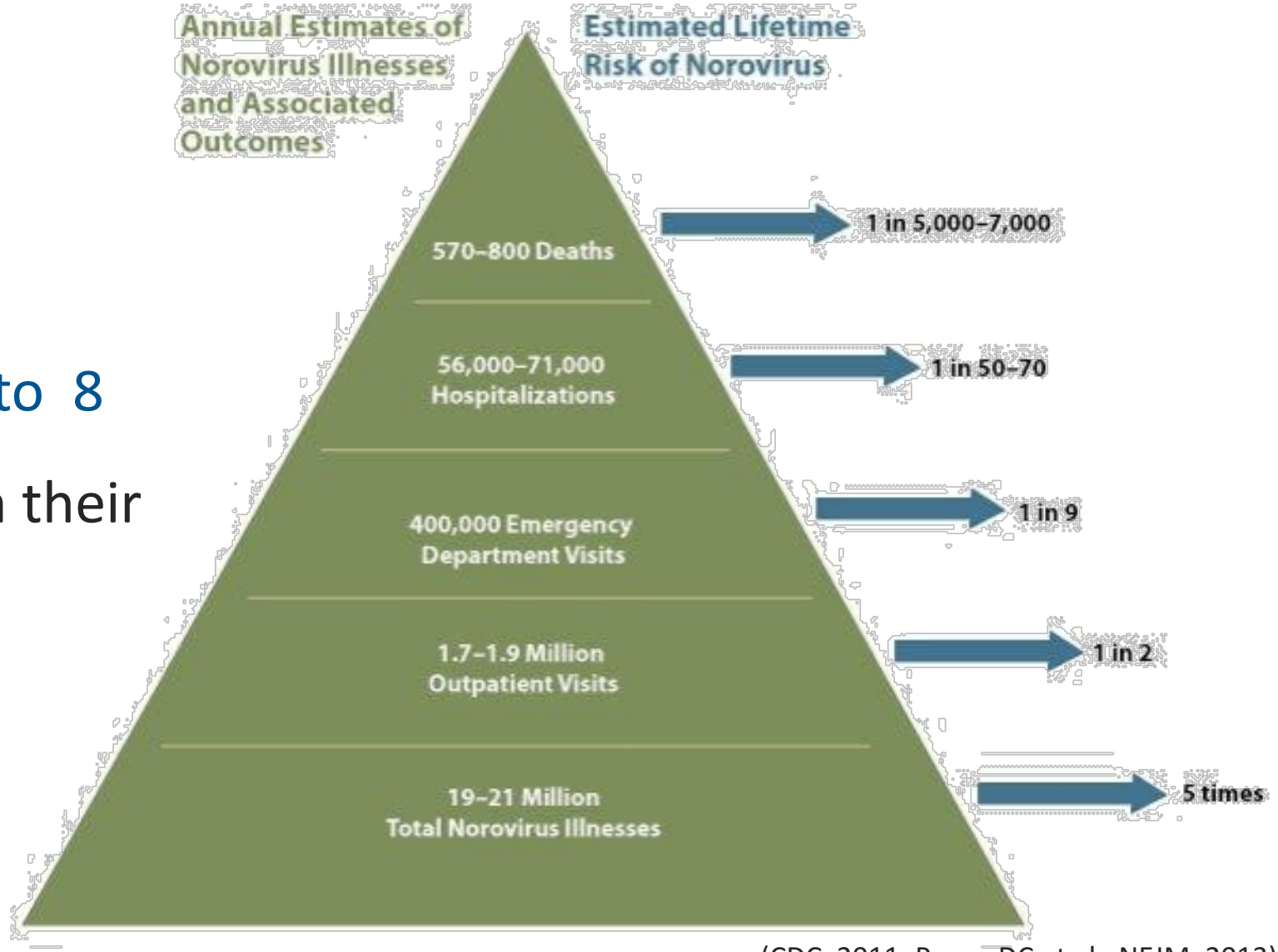
- Leading cause of acute gastroenteritis (AGE) across all ages especially children
- Symptoms: nausea, projectile vomiting and watery diarrhea
- Transmission route: fecal-oral route

(CDC, 2011; Payne DC et al., NEJM, 2013)

Burden of Norovirus Illness and Outbreaks

- No antivirals and vaccines available

- A person will experience 3 to 8 norovirus illness episodes in their lifetime



(CDC, 2011; Payne DC et al., NEJM, 2013)

Gut microbiota X norovirus infections

2014

LETTER

doi:10.1038/nature13960

An enteric virus can replace the beneficial function of commensal bacteria

Elisabeth Kernbauer[1,2], Yi Ding[3,4] & Ken Cadwell[1,2]

2014

NOROVIRUS

Enteric bacteria promote human and mouse norovirus infection of B cells

Melissa K. Jones,[1*] Makiko Watanabe,[1*] Shu Zhu,[1] Christina L. Graves,[2,3] Lisa R. Keyes,[1] Katrina R. Grau,[1] Mariam B. Gonzalez-Hernandez,[4] Nicole M. Iovine,[5] Christiane E. Wobus,[4] Jan Vinjé,[6] Scott A. Tibbetts,[1] Shannon M. Wallet,[2,3] Stephanie M. Karst[1†]

2015

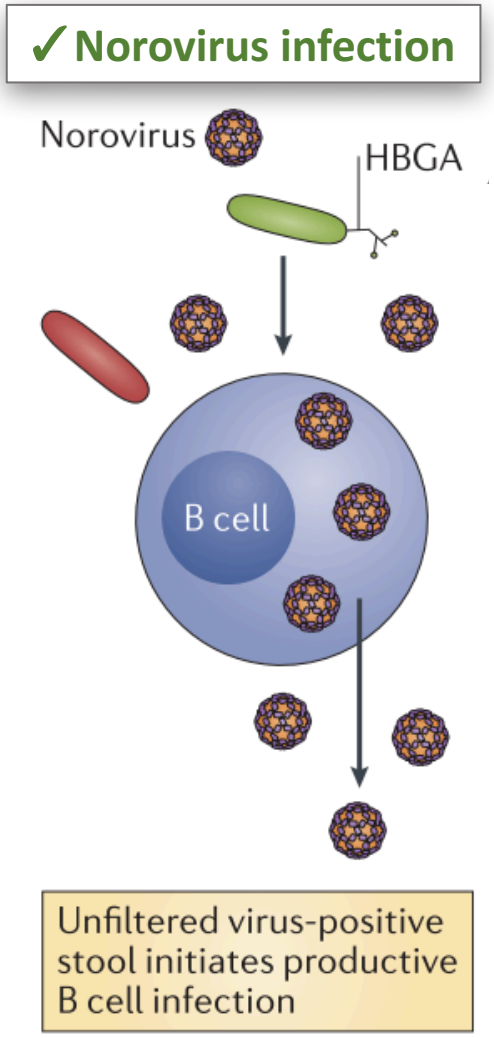
NOROVIRUS

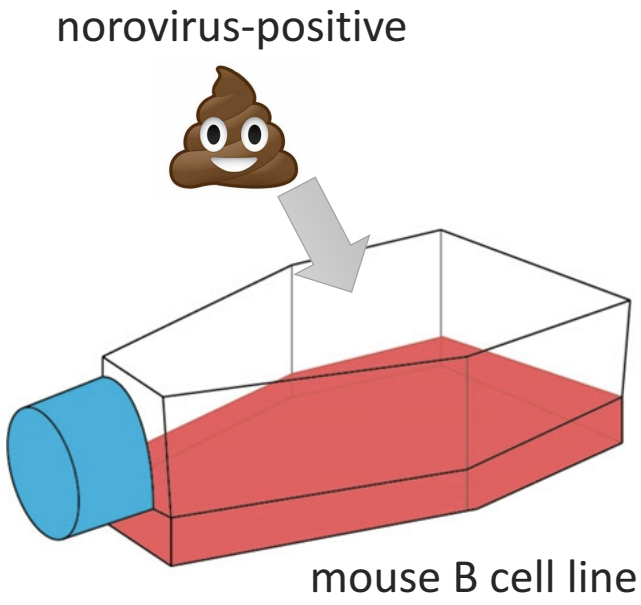
Commensal microbes and interferon-λ determine persistence of enteric murine norovirus infection

Megan T. Baldridge,[1] Timothy J. Nice,[1] Broc T. McCune,[1] Christine C. Yokoyama,[1] Amal Kambal,[1] Michael Wheadon,[1] Michael S. Diamond,[1,2] Yulia Ivanova,[1] Maxim Artyomov,[1] Herbert W. Virgin[1*]

Gut microbiota—friend of norovirus

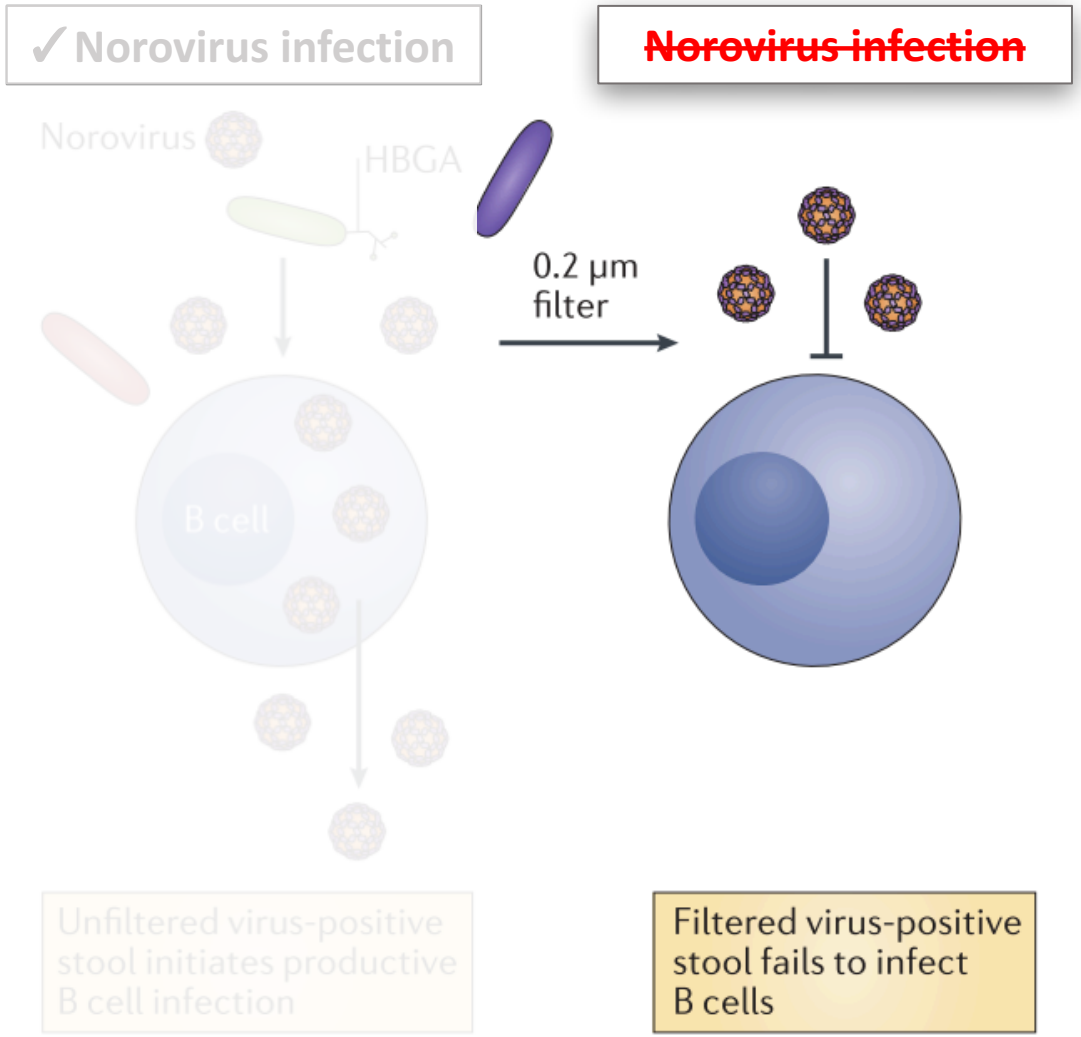
Gut microbiota can promote norovirus infection

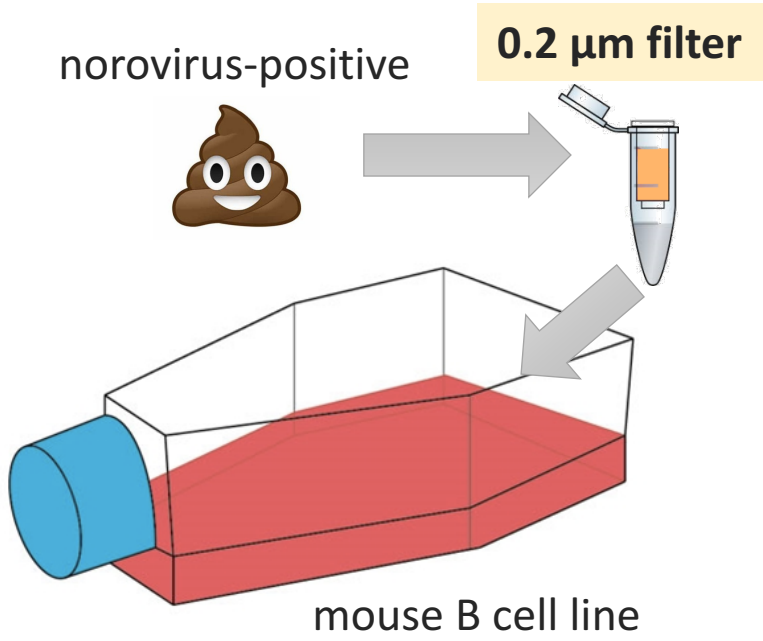




(Karst SM, Nature Reviews Microbiology, 2016)

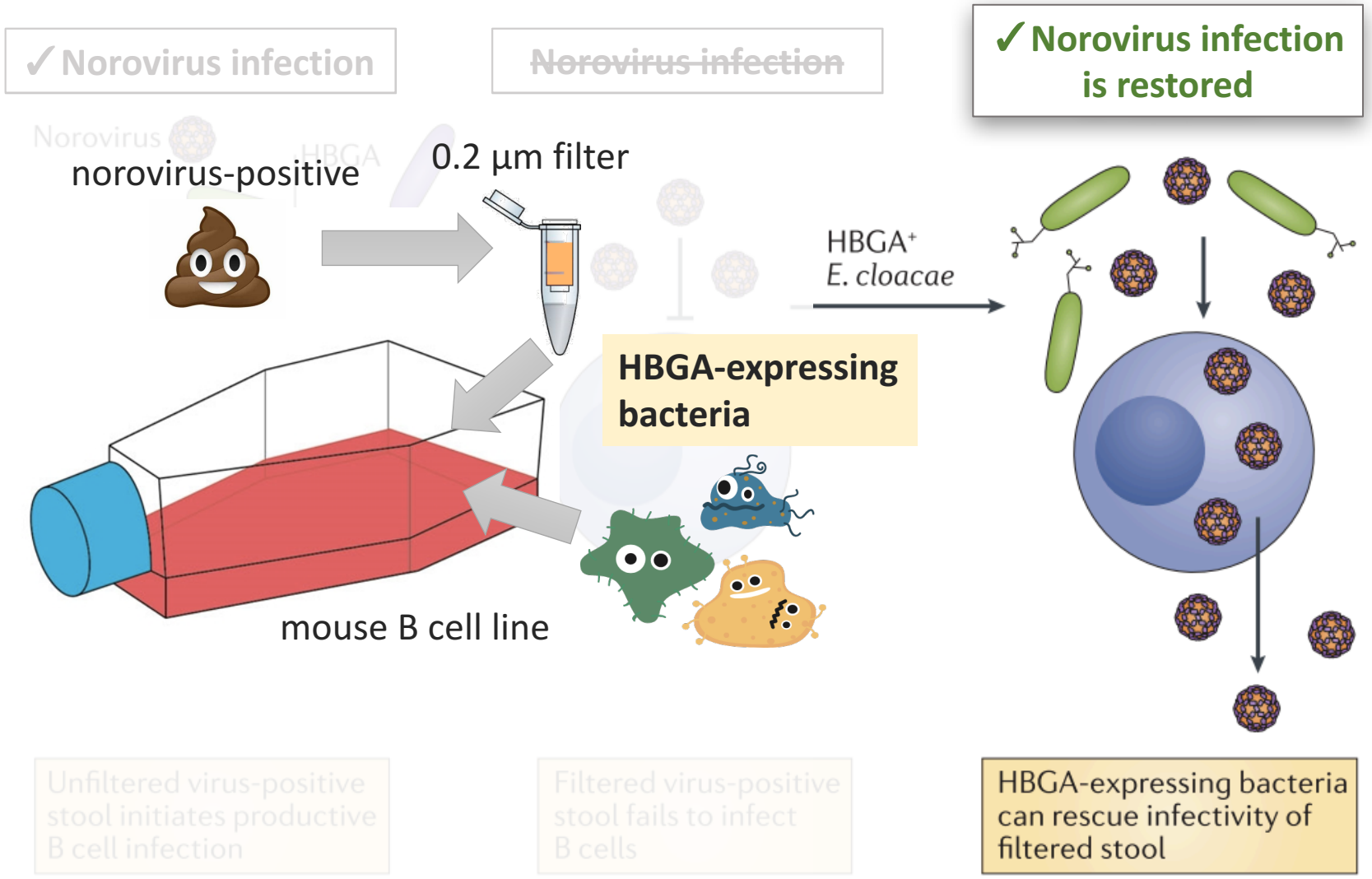
Gut microbiota can promote norovirus infection





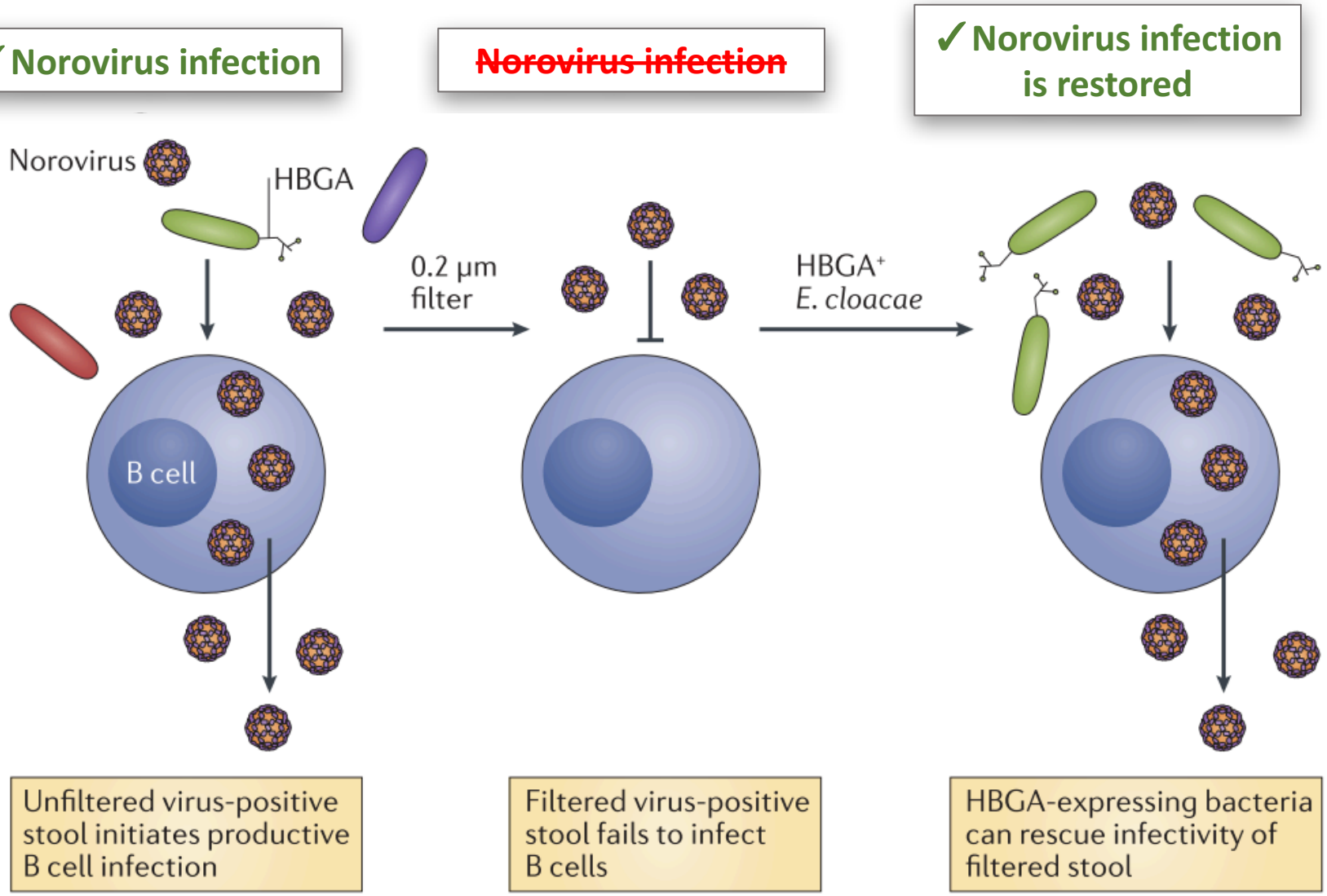
(Karst SM, Nature Reviews Microbiology, 2016)

Gut microbiota can promote norovirus infection



(Karst SM, Nature Reviews Microbiology, 2016)

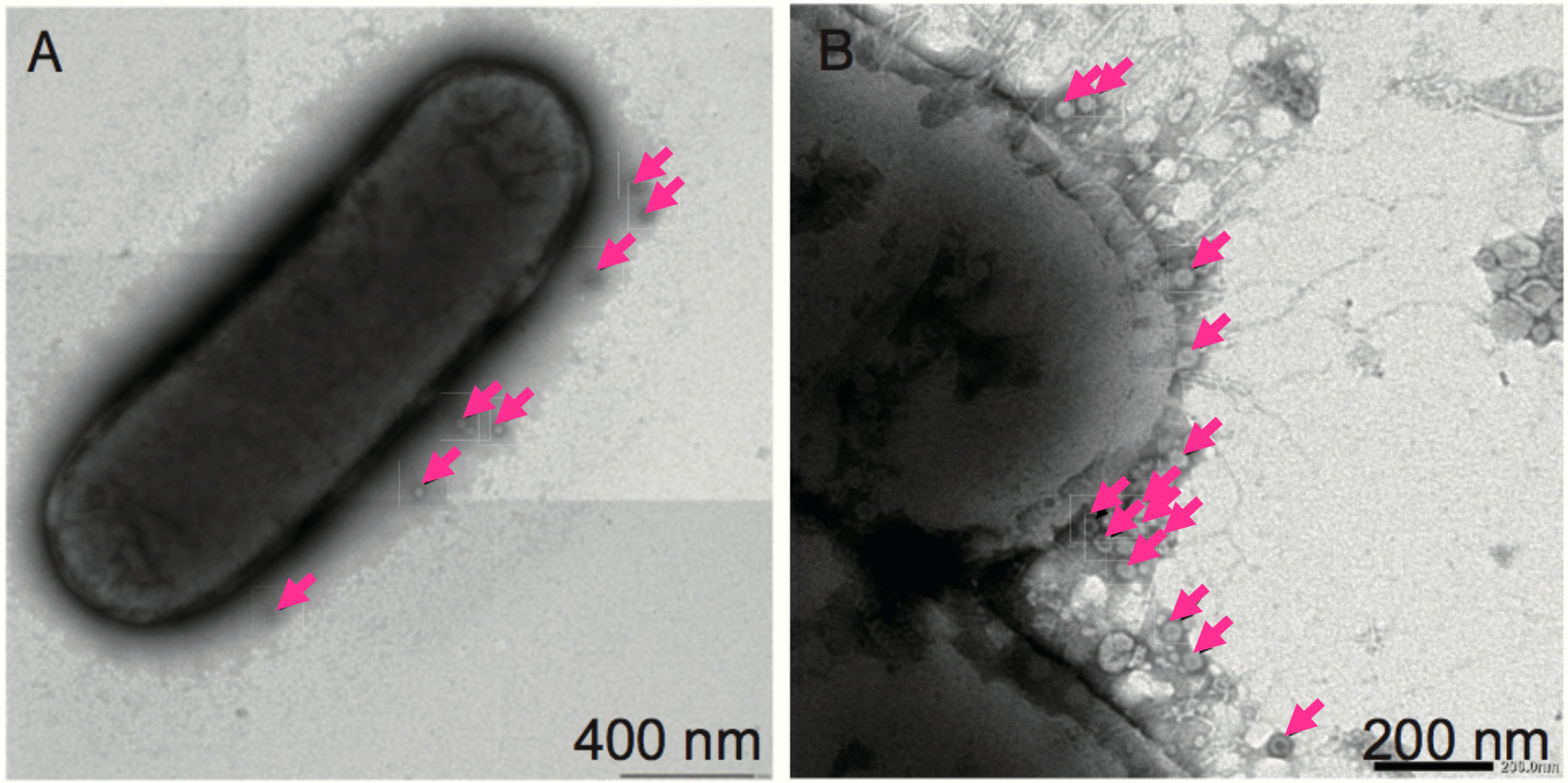
Gut microbiota can promote norovirus infection



(Karst SM, Nature Reviews Microbiology, 2016)

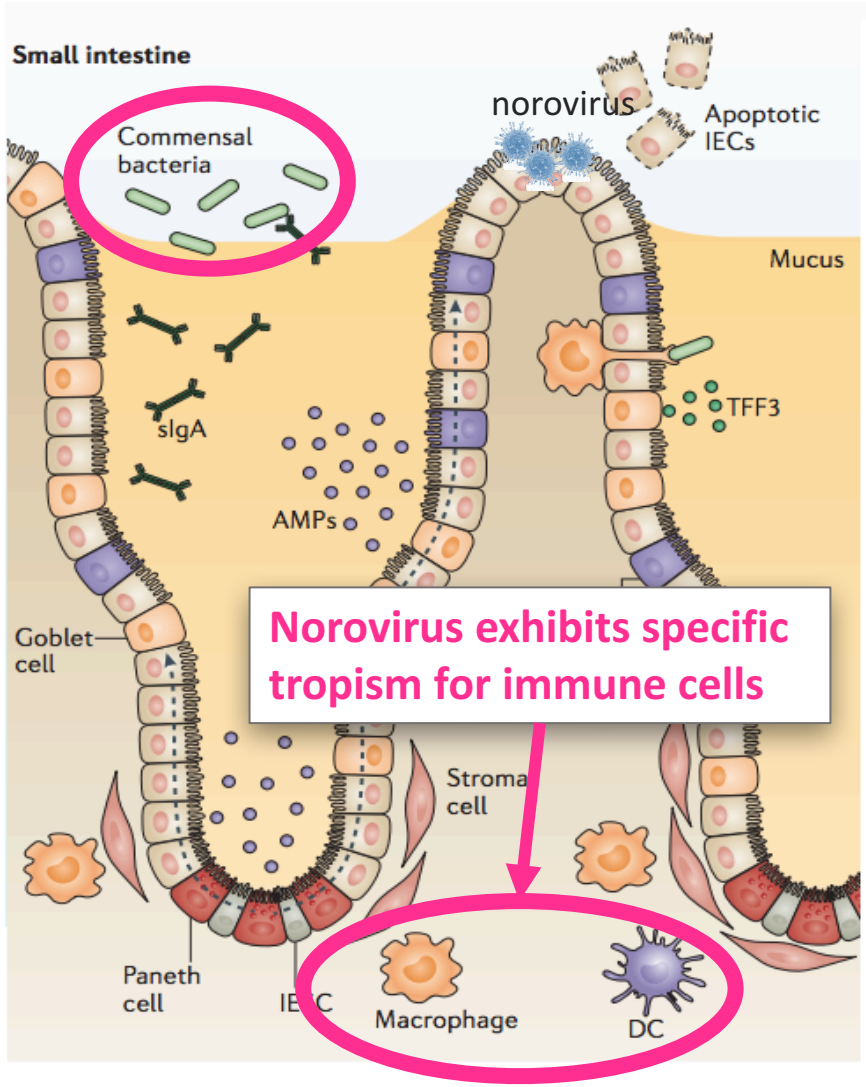
Commensal bacteria-norovirus interaction

Binding of **norovirus virus-like particles** to bacterial cells and localization of **HBGA-like substances of *Enterobacter* sp. SENG-6**



(Miura T et al., Journal of Virology, 2013)

How does norovirus-commensal bacteria binding stimulate viral attachment to host cells in the intestinal tract?



(Peterson LW et al., Nature Reviews Immunology, 2014)

- A thick mucus layer maintains a physical separation between the epithelium and commensal bacteria
- Norovirus exhibits specific tropism for immune cells

Possible explanations

- HBGA glycan (norovirus receptor): extracellular polymeric substance → secrete to gut lumen by bacteria
- Norovirus can bind to secreted outer membrane vesicles
- Virus–bacteria–host cell interactions may occur preferentially at sites of reduced host defences

(Karst SM, Nature Reviews Microbiology, 2016)

Gut microbiota can promote norovirus attachment

Norovirus can interact with bacterial surface glycans (HBGA)

✓ Enhance virion stability

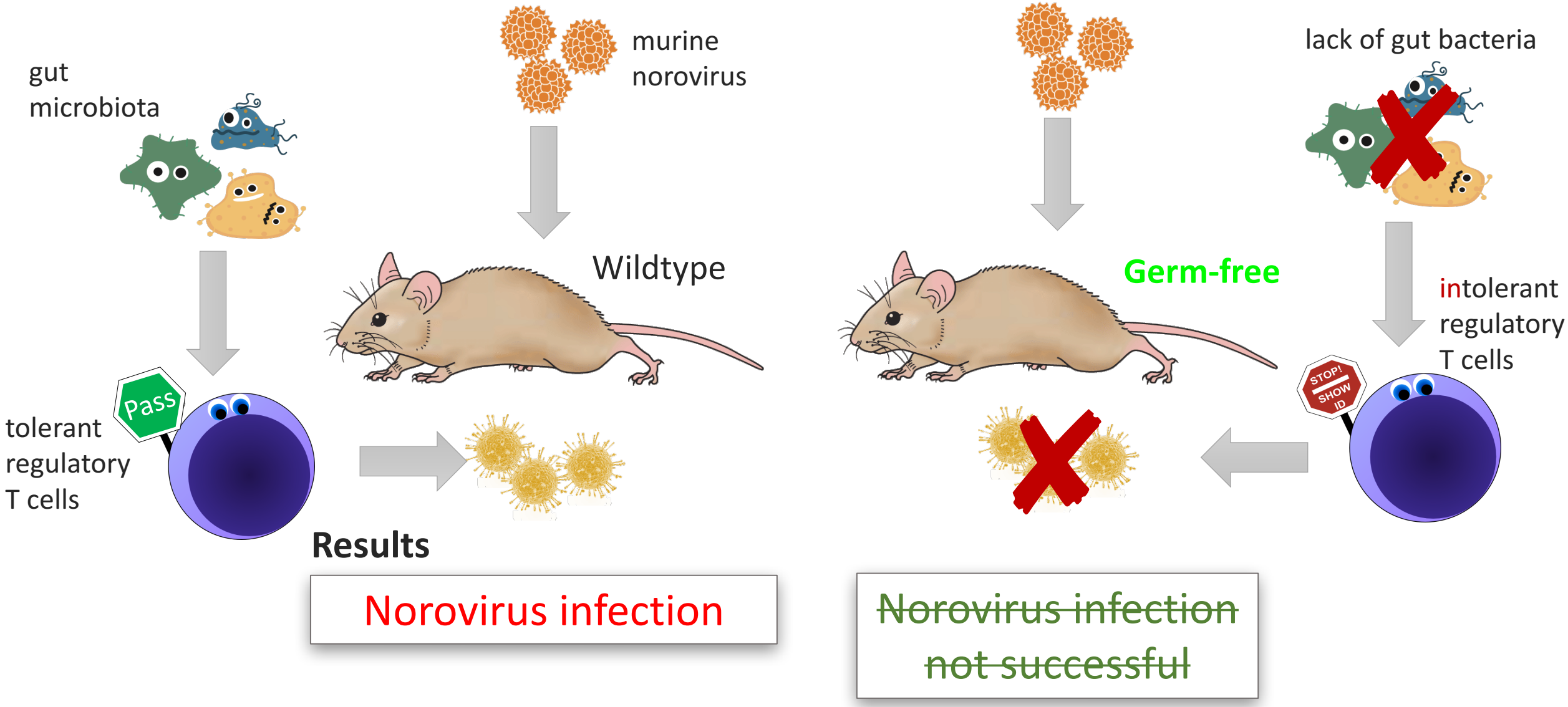
✓ Enhance binding to the surface of target host cells

✓Enhance norovirus infection directly

(Karst SM, Nature Reviews Microbiology, 2016)

Gut microbiota can enhance norovirus infection indirectly

Gut microbiota can promote norovirus infections indirectly



(Basic M et al., IBS, 2014)

Gut microbiota can induce a tolerogenic microenvironment

Possible explanation

Regulatory T cells

→maintain immunological tolerance to non-pathogenic microorganisms that comprise gut microbiota

→suppress other cell types in an antigen-nonspecific manner

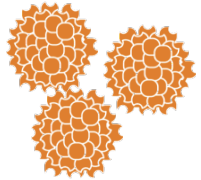
→✓**bystander suppression** of antiviral immune responses

✓Enhance norovirus infection indirectly

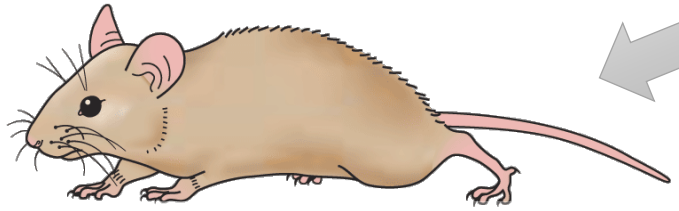
(Karst SM, Nature Reviews Microbiology, 2016)

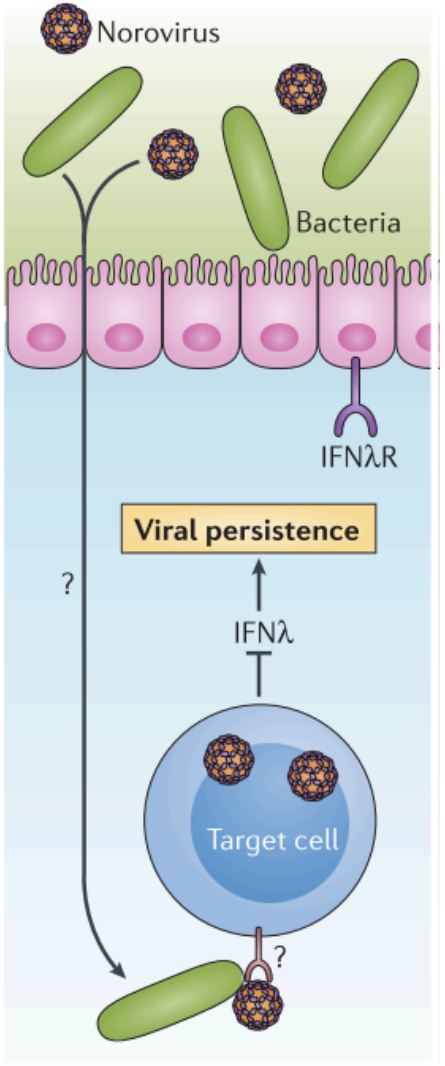
Gut microbiota can suppress IFN signaling

Condition 1: Wild-type colonized mice



murine norovirus





Norovirus-bacteria interaction

→ IFNλ production ↓

→ IFNλR receptor remains inactivated

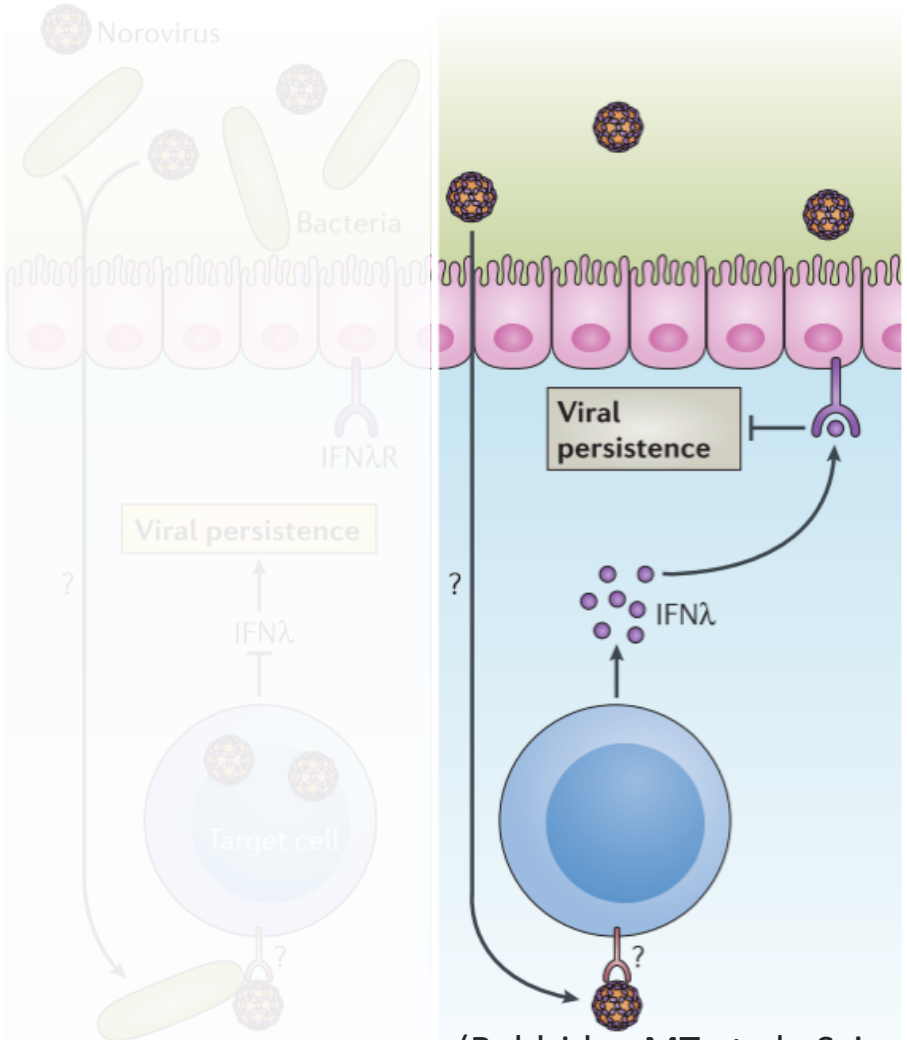
Results

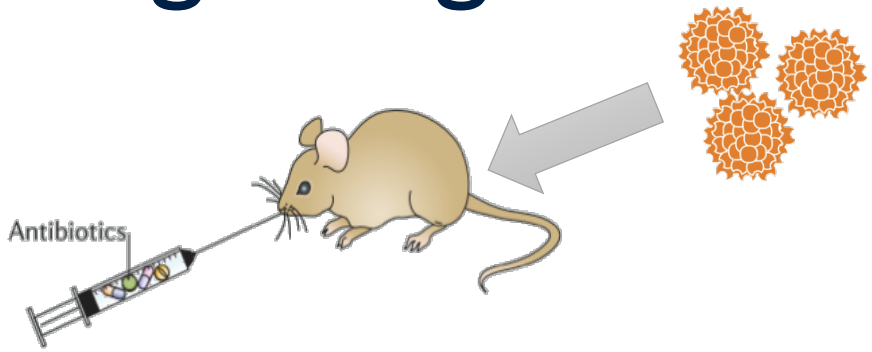
✓ **Viral persistence**

(Baldridge MT et al., Science, 2015; Karst SM et al., Nature Reviews Microbiology,2016)

Gut microbiota can suppress IFN signaling

Condition 2: Wild-type antibiotic-treated mice





Antibiotic treatment

→ ✘ bacteria

→ ✓ IFNλ production

→ IFNλR receptor was activated by IFN λ

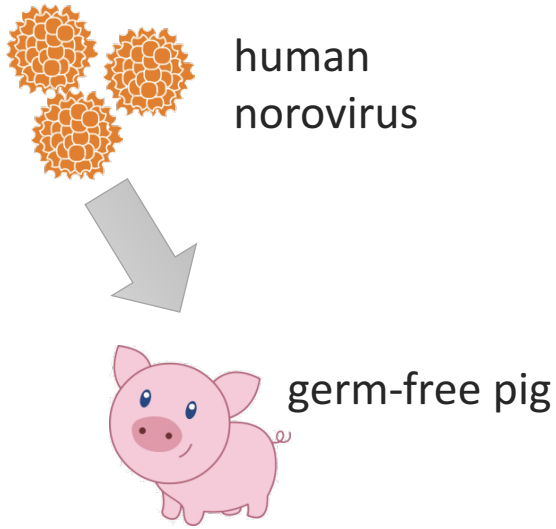
Results

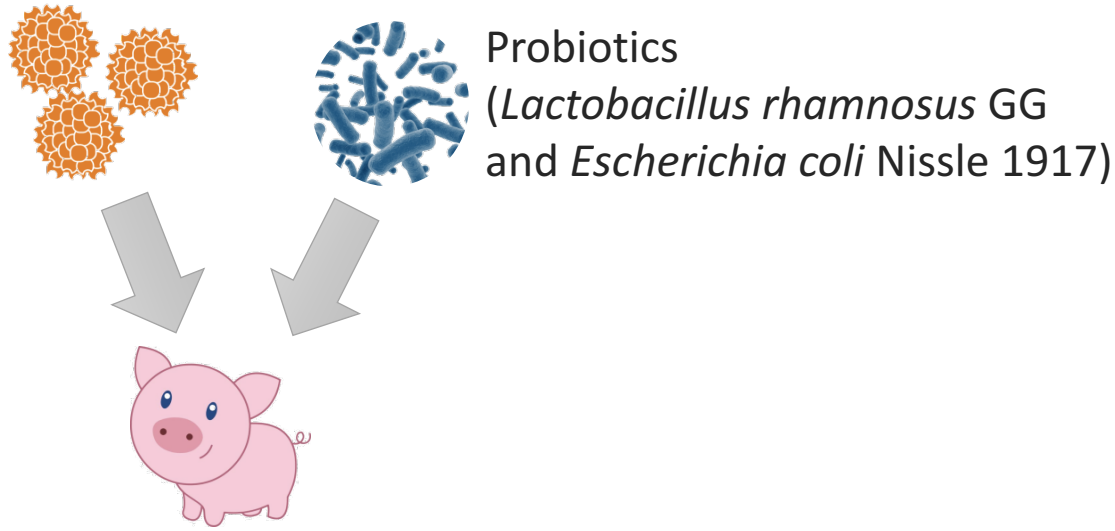
~~✘ Viral persistence~~

(Baldridge MT et al., Science, 2015; Karst SM et al., Nature Reviews Microbiology,2016)

Gut microbiota—foe of norovirus

Probiotics inhibit norovirus infections in germ-free pigs





Results

✓Virus shedding
✓diarrhea

Incidence ↓
Virus shedding ↓
Duration of diarrhea ↓
Diarrhea severity ↓

(Lei S et al., Front Microbiol, 2016)

Norovirus-gut microbiota interaction —

the complicated relationship

- Noroviruses have evolved diverse strategies to deal with the microorganisms they encounter in the gut lumen
- Certain commensal bacteria (e.g., those with HBGA glycans) can promote norovirus infection through direct and indirect interactions
- Non-pathogenic flora *(e.g. Lactobacillus)* can inhibit norovirus infection

Can we prevent and treat norovirus infections by manipulating gut microbiota?

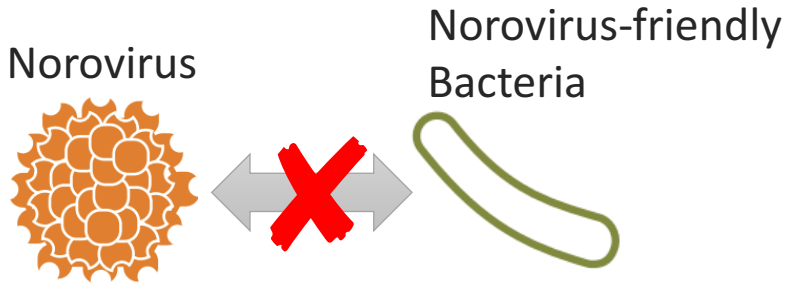
Norovirus-commensal bacteria interaction —

transkingdom control of norovirus infections

Possible approaches

- Design drugs that override the tolerogenic signal provided by the commensal bacterial antigens
- Disrupt norovirus-bacteria interaction
  - Use antibiotics to deplete bacteria?

  → Bacteria ↓ → Norovirus ↓



- Use non-pathogenic flora to inhibit norovirus infections

(Pfeiffer JK et al., Science, 2016)

research gaps and future challenges

- Lack of studies to investigate interactions between norovirus and other community of gut microbiota (e.g., phages, fungi & archaea etc.)
- Multiple factors (e.g. host factors) might contribute to virus-bacteria interactions that might affect data interpretation
- Is mouse model applicable to human norovirus infections?

Q&A

Image references

Slides #	Reference
5	https://c1.staticflickr.com/9/8092/8470104250_5a714c9863.jpg
6	https://www.cdc.gov/norovirus/images/eid-fig03.png
7	http://www.kasparov.com/wp-content/uploads/2017/05/nature-journal-559x280.jpg http://www.sciencemag.org/sites/all/themes/science/images/facebook-share.jpg
9-11	https://www.kerafast.com/images/Product/icon/1742.jpg https://cdn.shopify.com/s/files/1/1061/1924/products/Poop_Emoji_7b204f05-eec6-4496-91b1-351acc03d2c7_large.png?v=1480481059
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17	http://www.clker.com/cliparts/M/s/l/W/H/Y/cartoon-t-cell.svg https://openclipart.org/download/284321/publicdomainq-0004785mfacxt.svg
17,19,20,22	http://clipart-library.com/clipart/990049.htm Pfeiffer JK et al., Science, 2016
22	http://yaletownnaturopathic.com/wp-content/uploads/2015/05/best-probiotic-brand.jpg http://clipartix.com/wp-content/uploads/2017/07/Pig-clipart-pig.jpg
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