Acute Gastrointestinal Infections

Watery Diarrhea- Bacterial Pathogens

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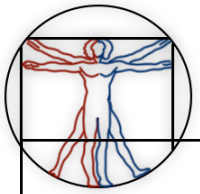
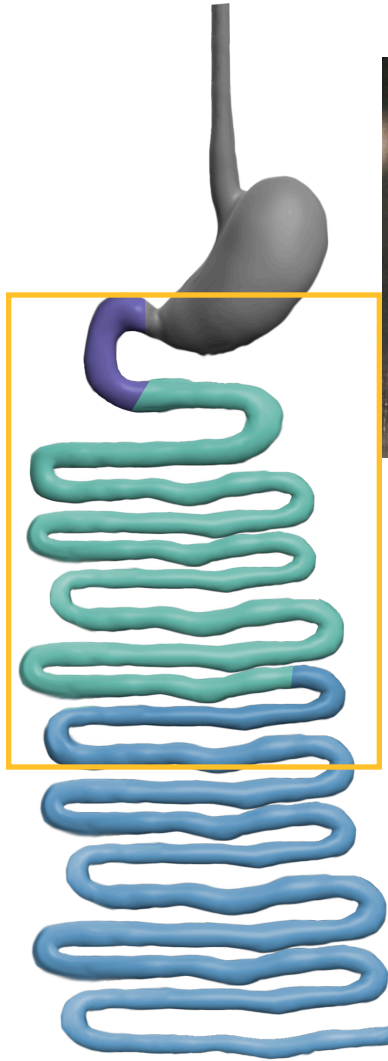
Learning Objectives

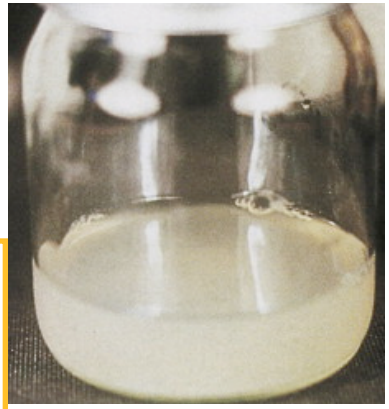
- Recognize the clinical features of Watery Diarrhea and how they relate to the pathogenesis of *Vibrio cholerae*, ETEC and EPEC.

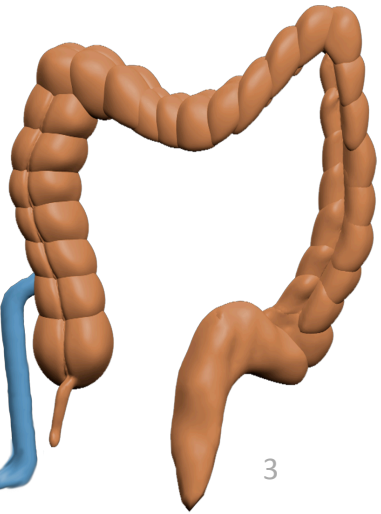


Watery Diarrhea

Clinical Features	Large volume watery stools without inflammatory cells or blood. Can lead to dehydration. Possibly accompanied by nausea, vomiting, bloating, colicky abdominal pain
Complications	Dehydration, electrolyte abnormalities, malnutrition
Management	Assess degree of dehydration, consider DDx, rehydrate, maintenance hydration
Anatomical Location	Proximal Small Intestine
Pathogenesis	Non-invasive, several are toxin mediated, secretory vs malabsorptive
Viruses	Rotavirus, Norovirus, Adenovirus (all non-enveloped capsids)
Bacteria	***Vibrio cholerae*, Enterotoxigenic *E. coli* (ETEC), EPEC, EAEC**
Protozoa	*Giardia*, *Cryptosporidium*

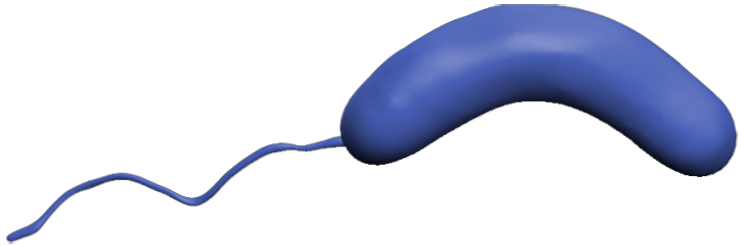






Vibrio cholerae

- *Vibrio cholerae* is a gram negative curved rod with a single flagellum at one end
- It has an aquatic environmental reservoir
- Related to *Vibrios* in the ocean. Many are commensals in the gut of fish and invertebrates.
  - Some are fish and invertebrate pathogens
  - *Vibrio vulnificus* and *V. parahaemolyticus* can cause gastroenteritis in humans from shellfish.
- A few strains of *Vibrio cholerae* are highly adapted to the human host and cause outbreaks, epidemics and pandemics



Vibrio cholerae causes cholera

- *Vibrio cholerae* can cause severe diarrhea
  - up to 1 liter liquid stool per hour
    - rapid dehydration
    - shock and death within a few hours
- Untreated 30% mortality, but with adequate medical care <1% mortality
- Outbreaks from fecal-oral transmission
  - contamination of water
  - natural catastrophes, political instability, poverty
- Diagnosis
  - Microscopy examination of stool
  - Definitive diagnosis with stool culture
- Antibiotics can decrease stool output by 50%

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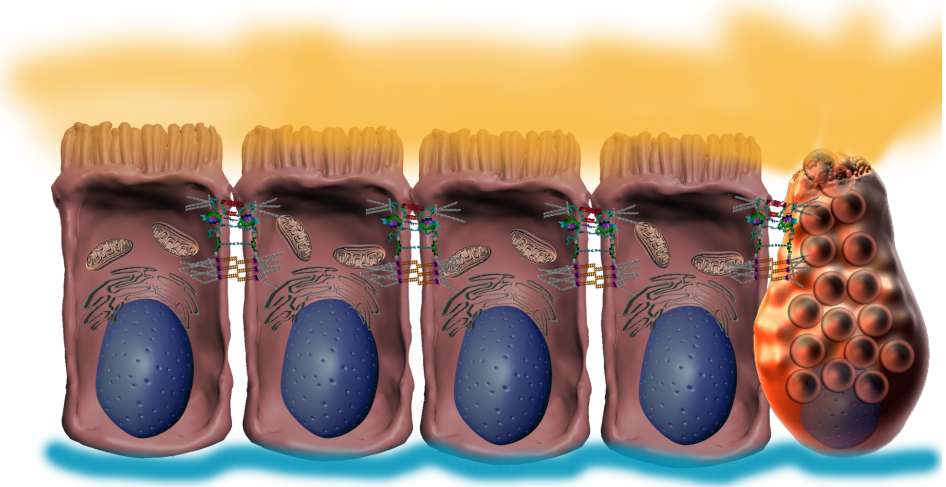
Cholera pathogenesis

- A large inoculum is required to cause disease (about 10^8).
  - Sensitive to acid in stomach
- Colonizes the small intestine
- Flagellar motility- darting motility
- Produce mucinases that degrade mucus
- Attach to epithelium via TCP pili-
- Bacteria multiply on the surface of the villi
- Toxin production leads to secretory diarrhea and to dispersal and exit of the bacteria



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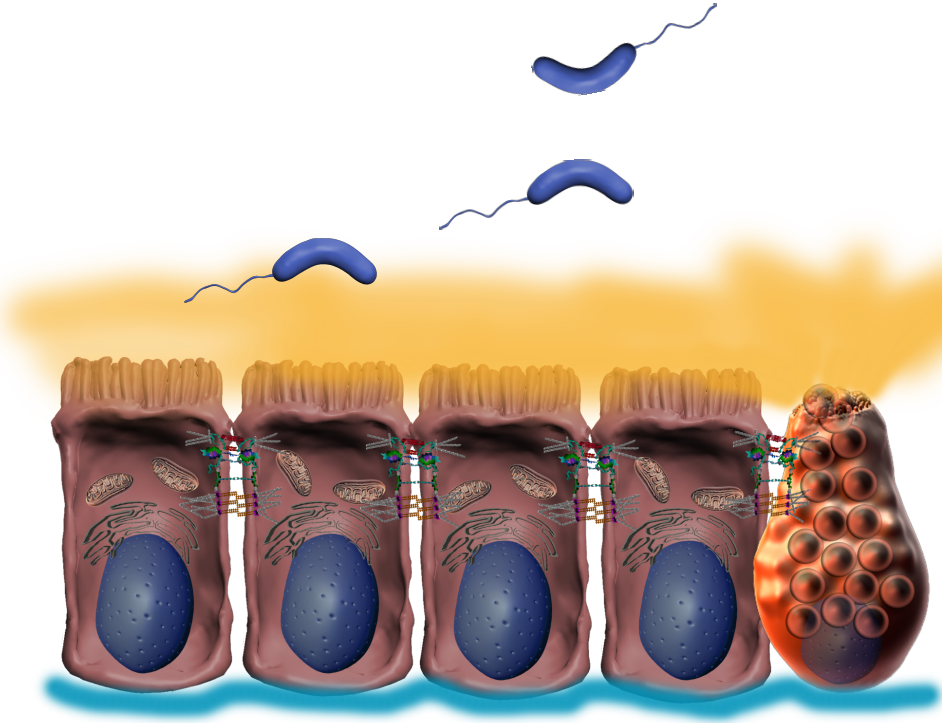

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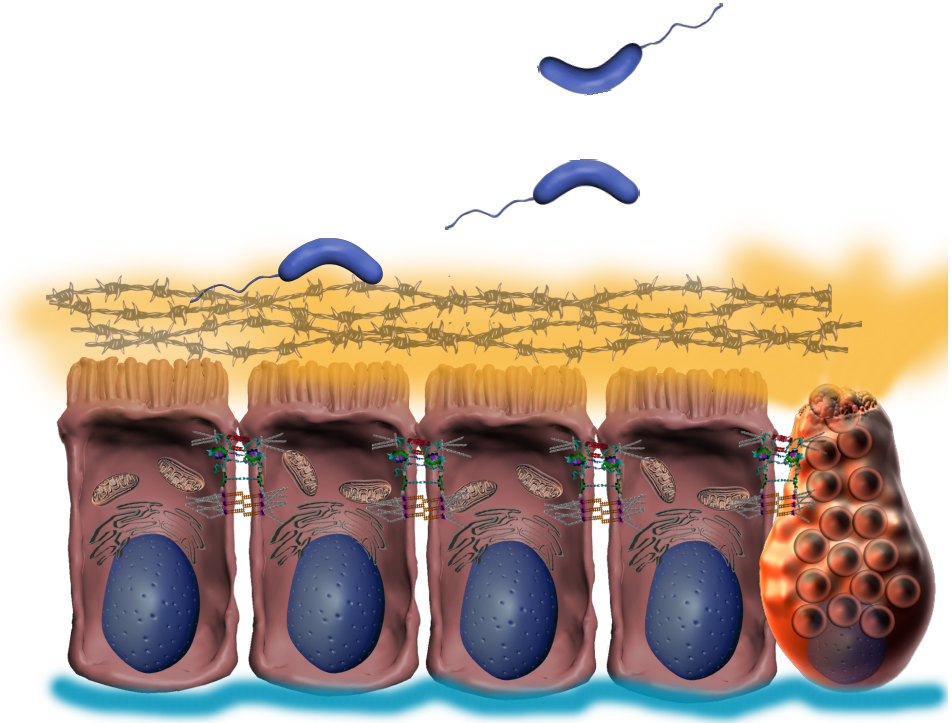

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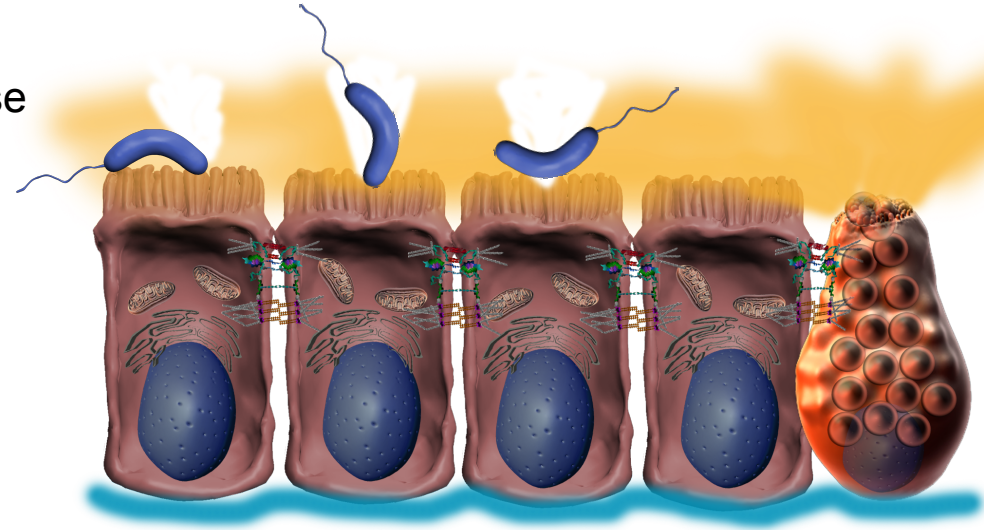

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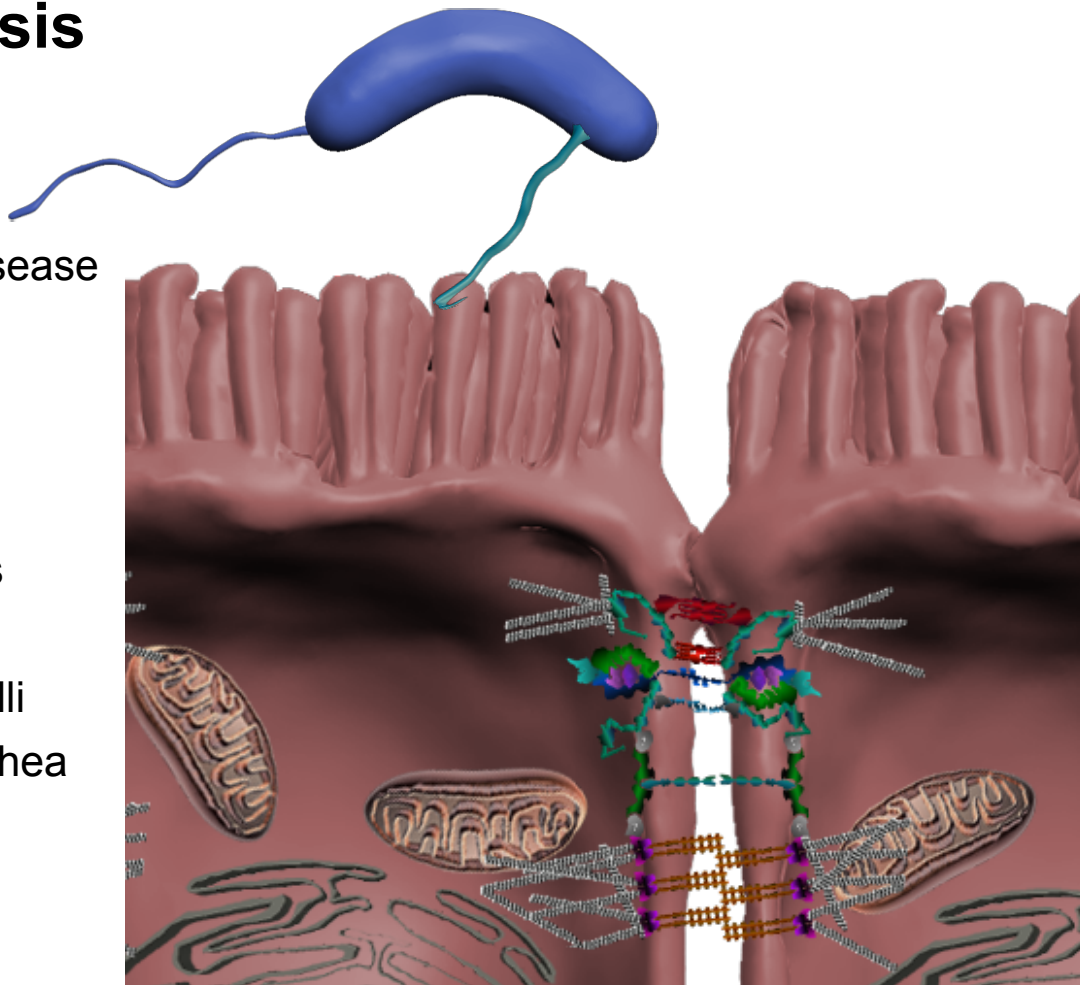

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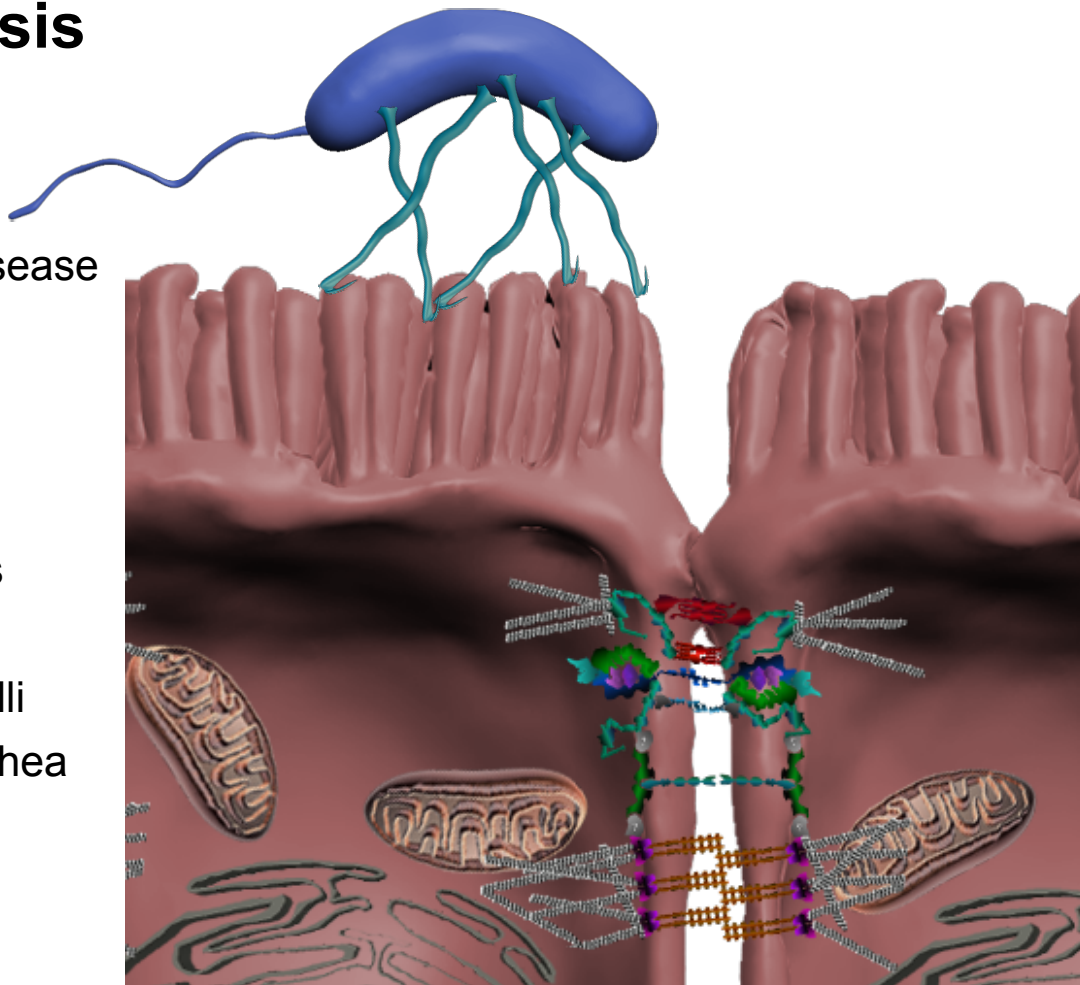

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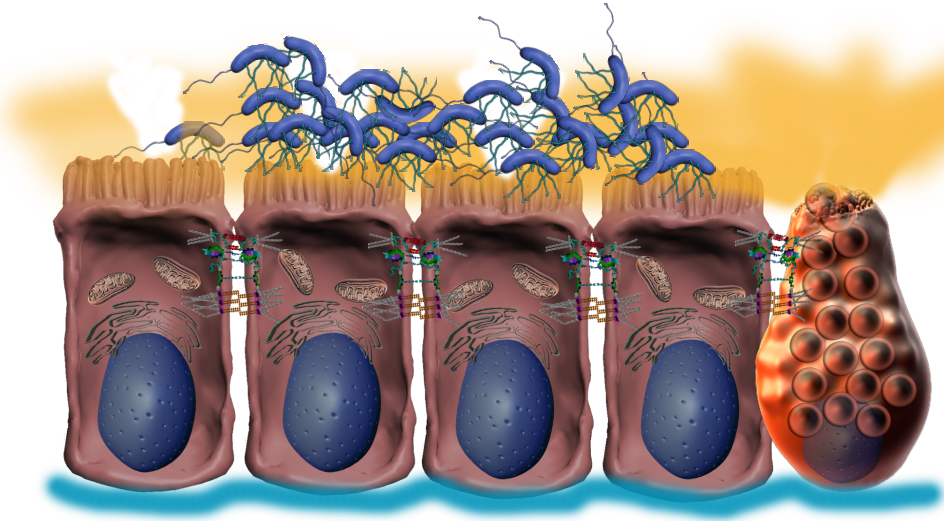

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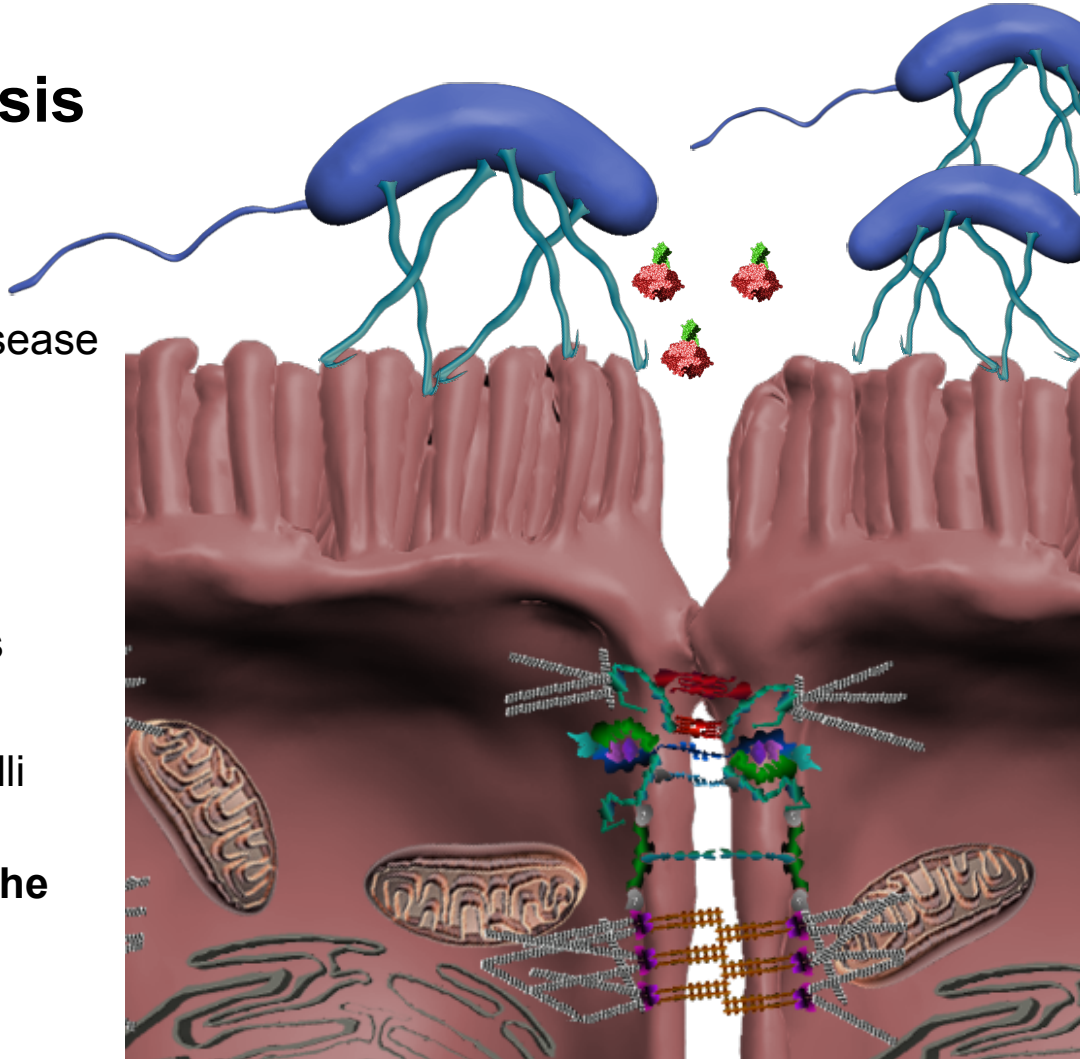

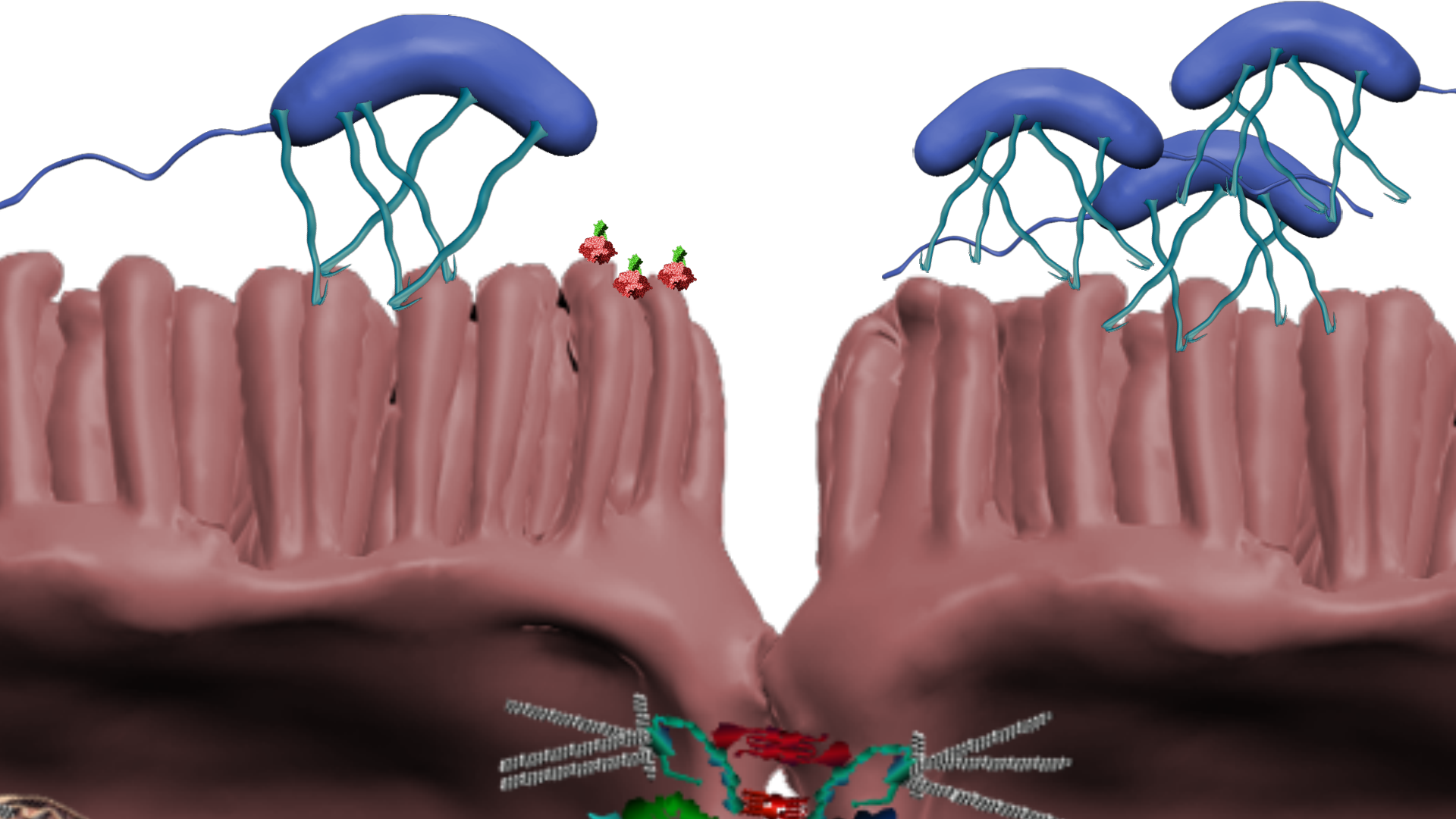

Cholera toxin mechanism

- Cholera toxin is an **A-B toxin**
  - **B**- “binding” subunit binds to the surface of enterocytes by attaching to its receptor: ganglioside **GM1**
  - **A**- “active” is an enzyme that modifies and activates G-proteins when introduced into the cytosol

- Several important bacterial toxins are AB-toxins
  - LT-toxin from EPEC
  - Shiga toxin- Shigella, StEC
  - Pertussis toxin (whooping cough),
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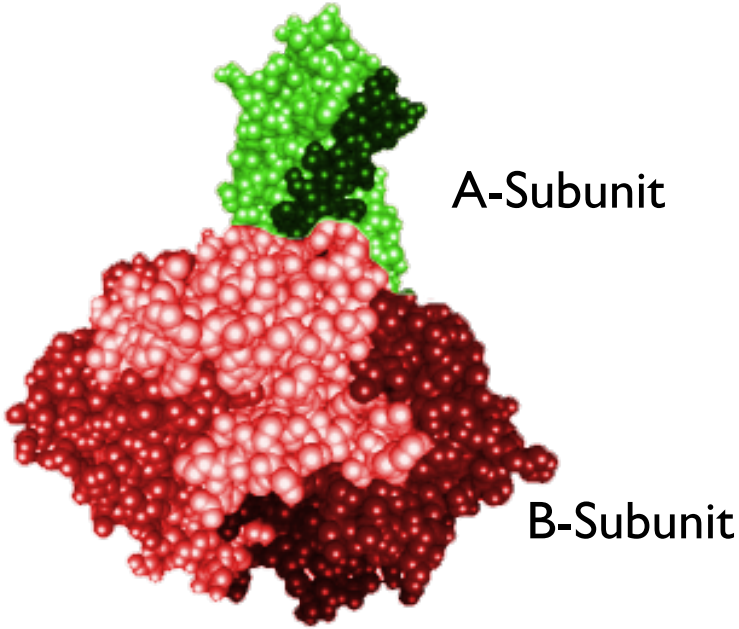

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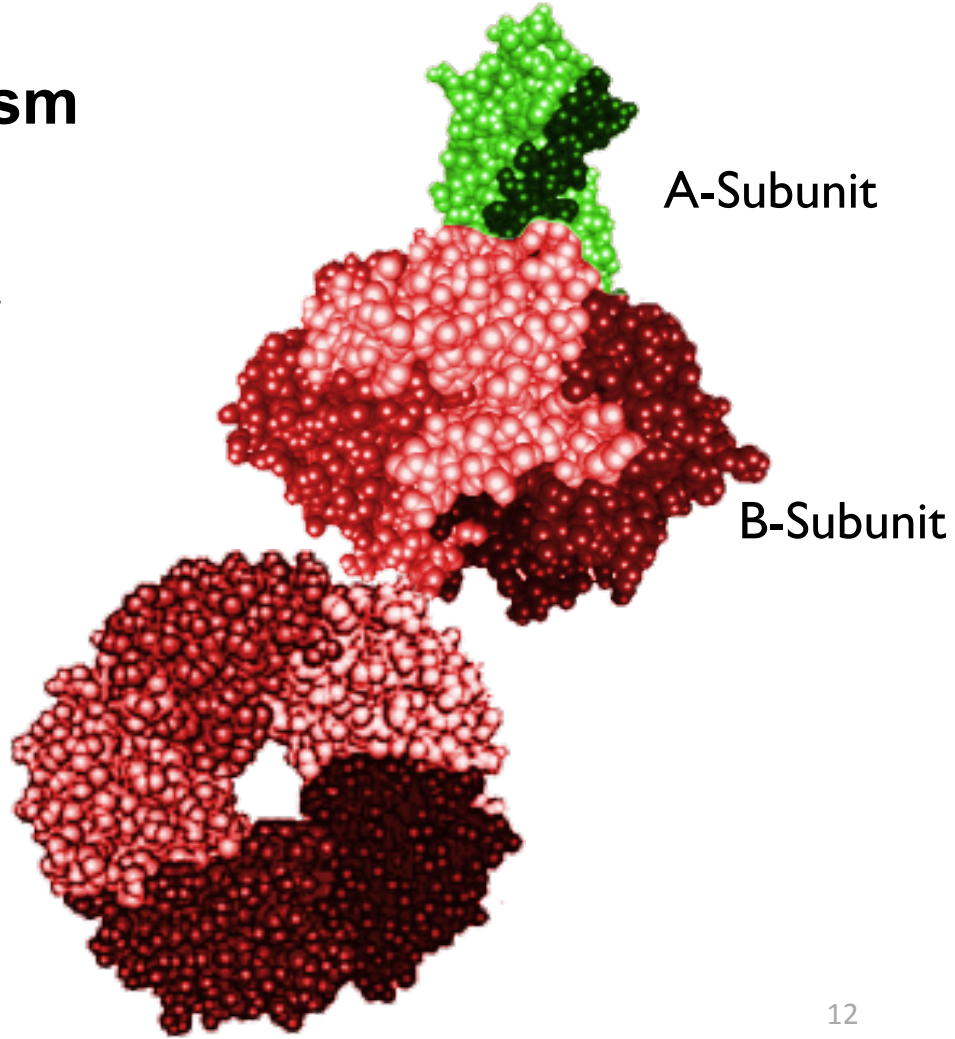

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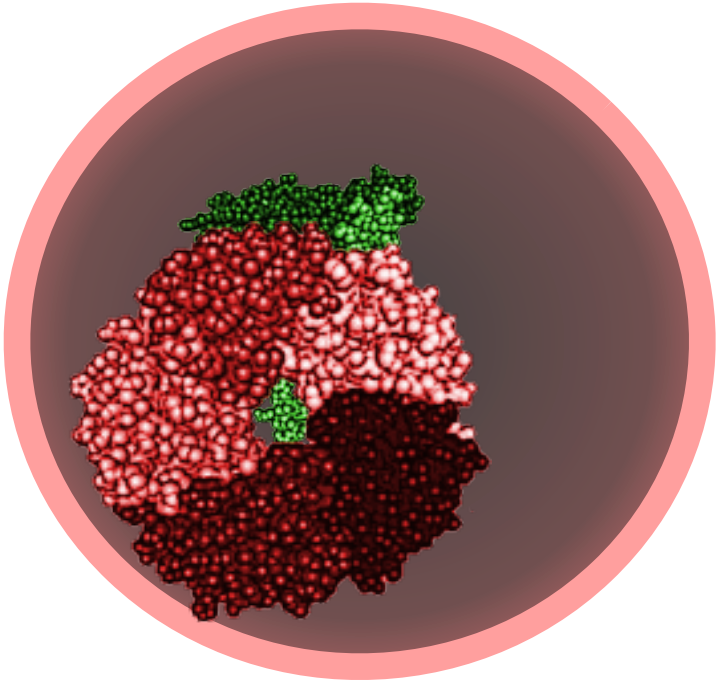
- Binding of the B-subunit GM1 leads to internalization of the toxin by endocytosis
- Acidification of the vacuole allows for separation of the two subunits
- The A-subunit is translocated into the cytosol through a pore formed by the ring-like B-subunit



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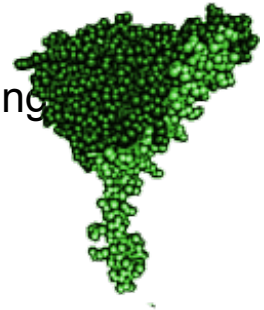
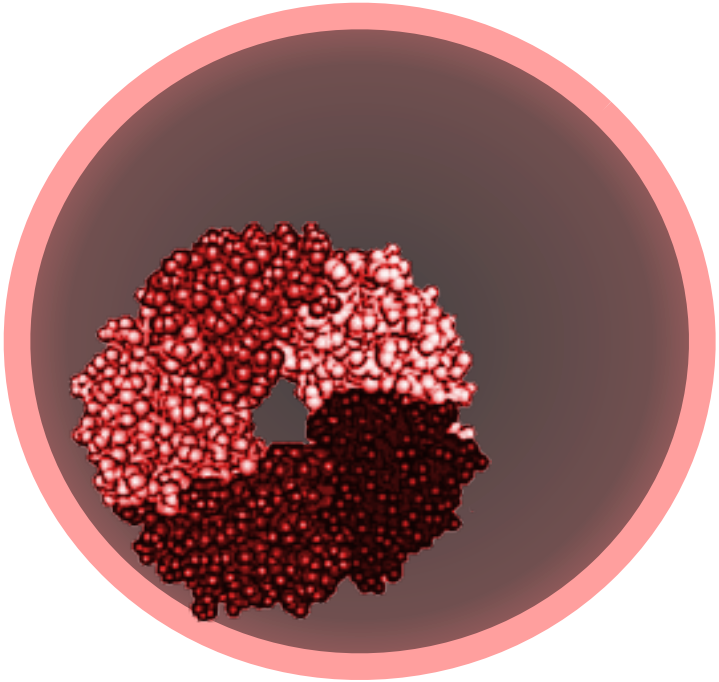
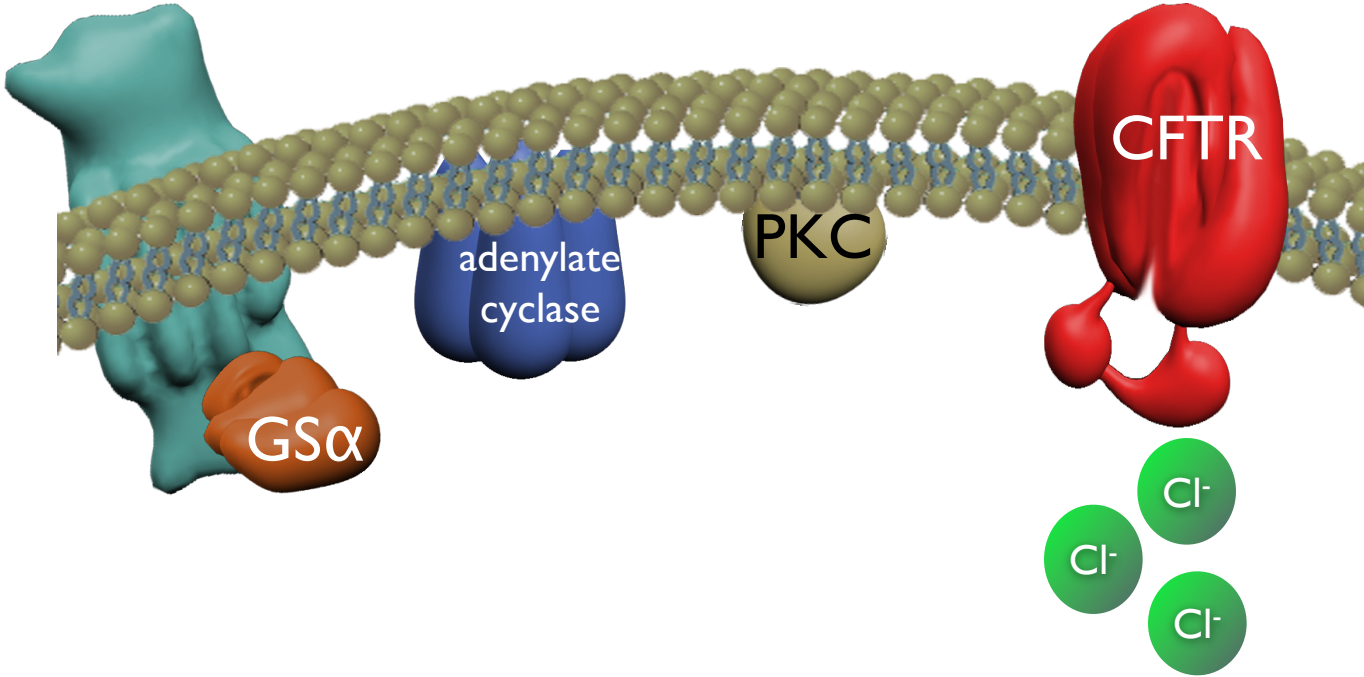




Cholera toxin mechanism

- Cholera Toxin-A ADP-ribosylates Gs increases adenylate cyclase activity and cAMP
- Endpoint is phosphorylation and opening of chloride channel- CFTR



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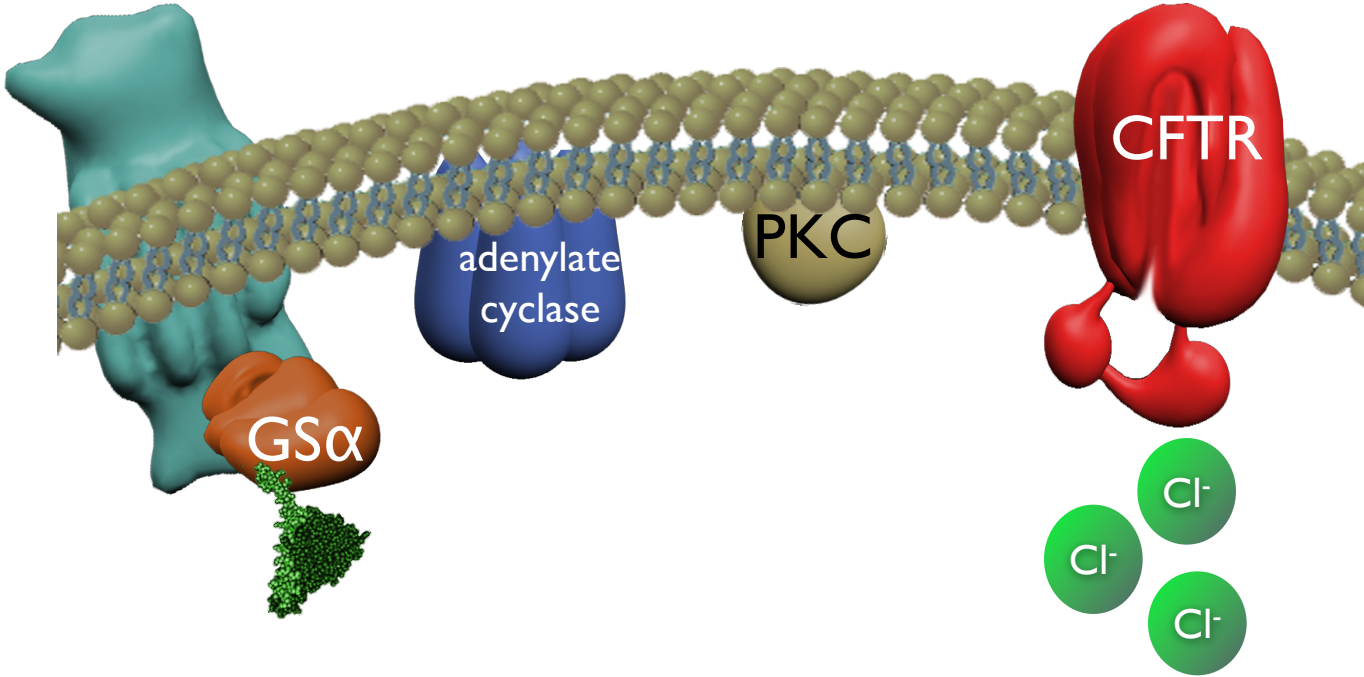

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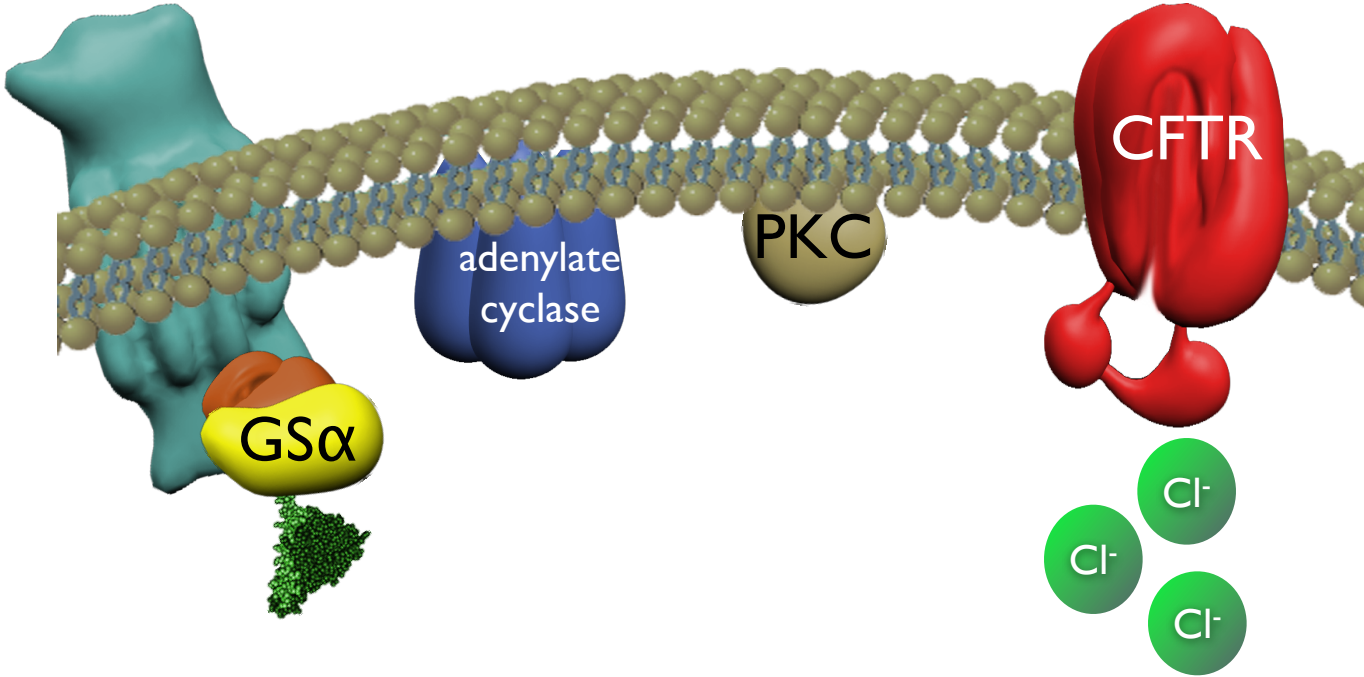

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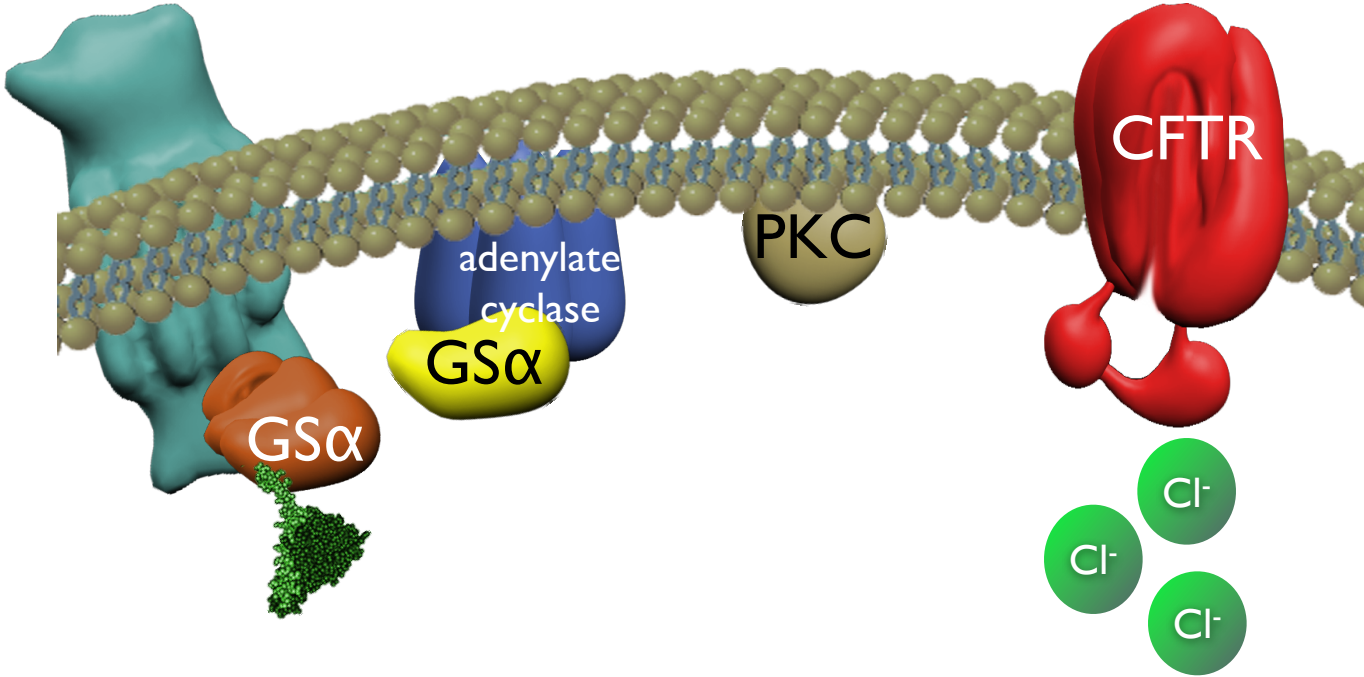

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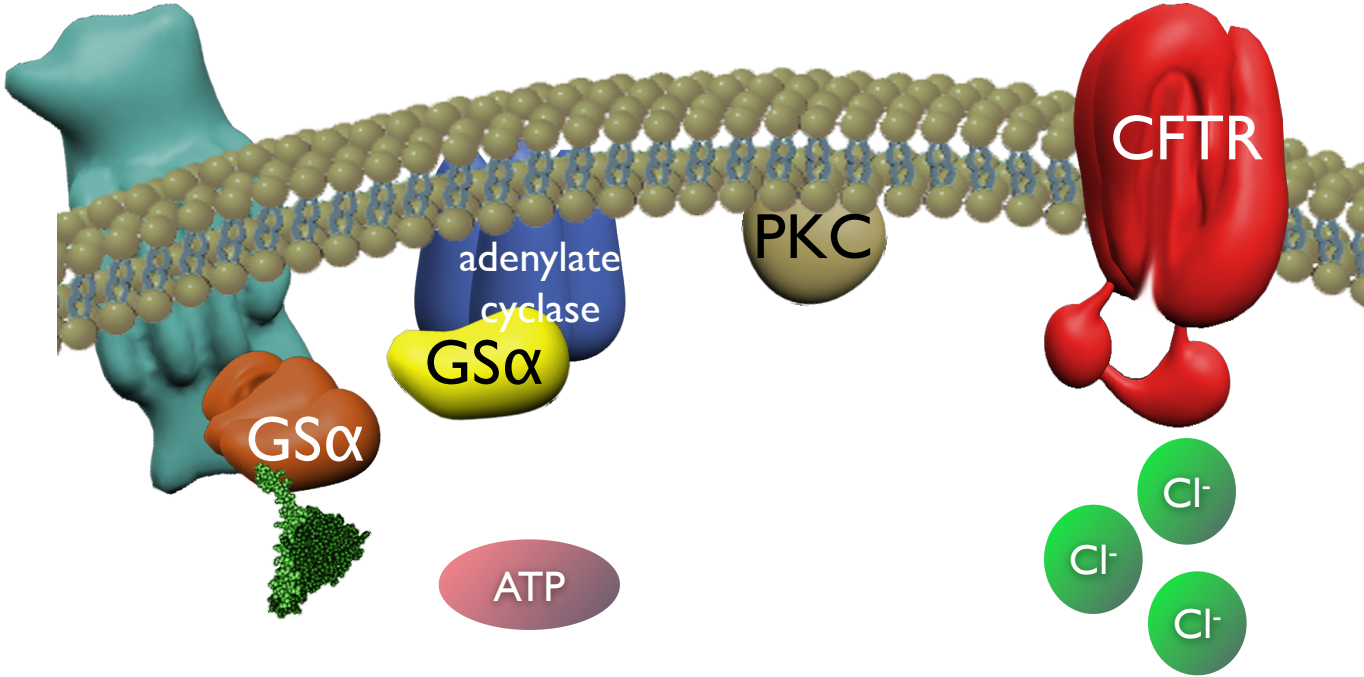

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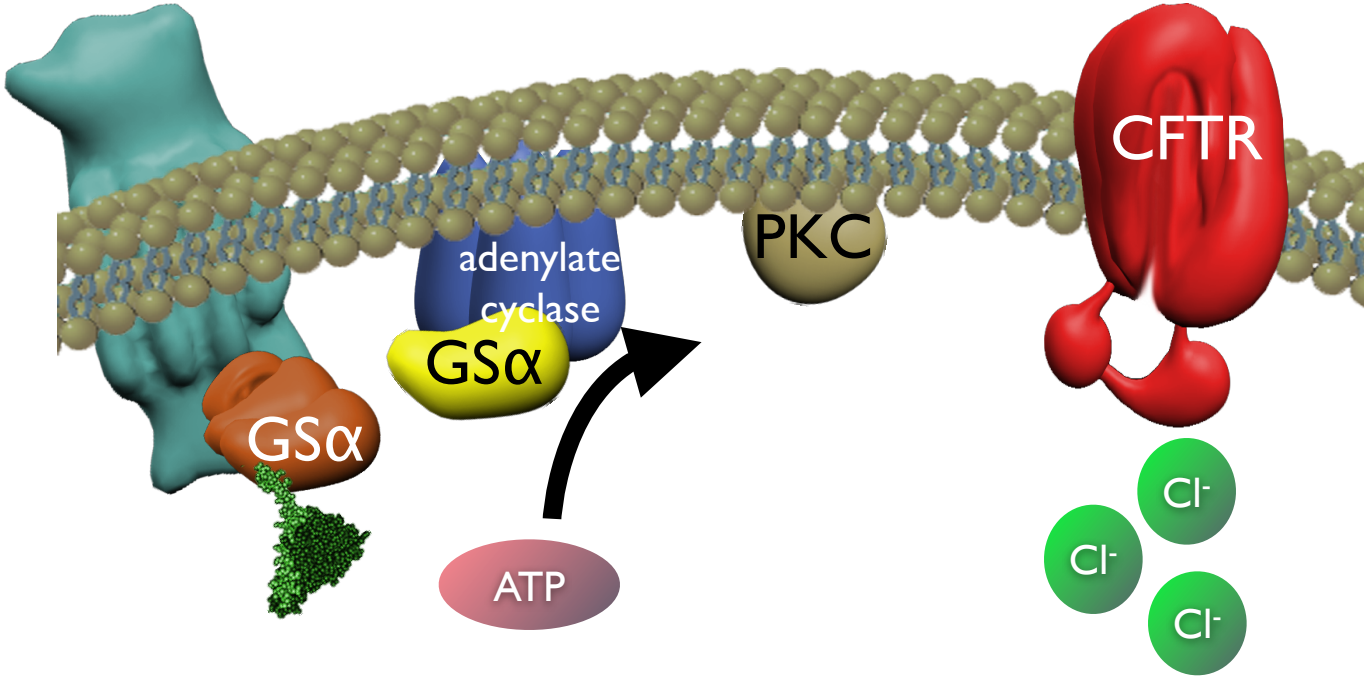

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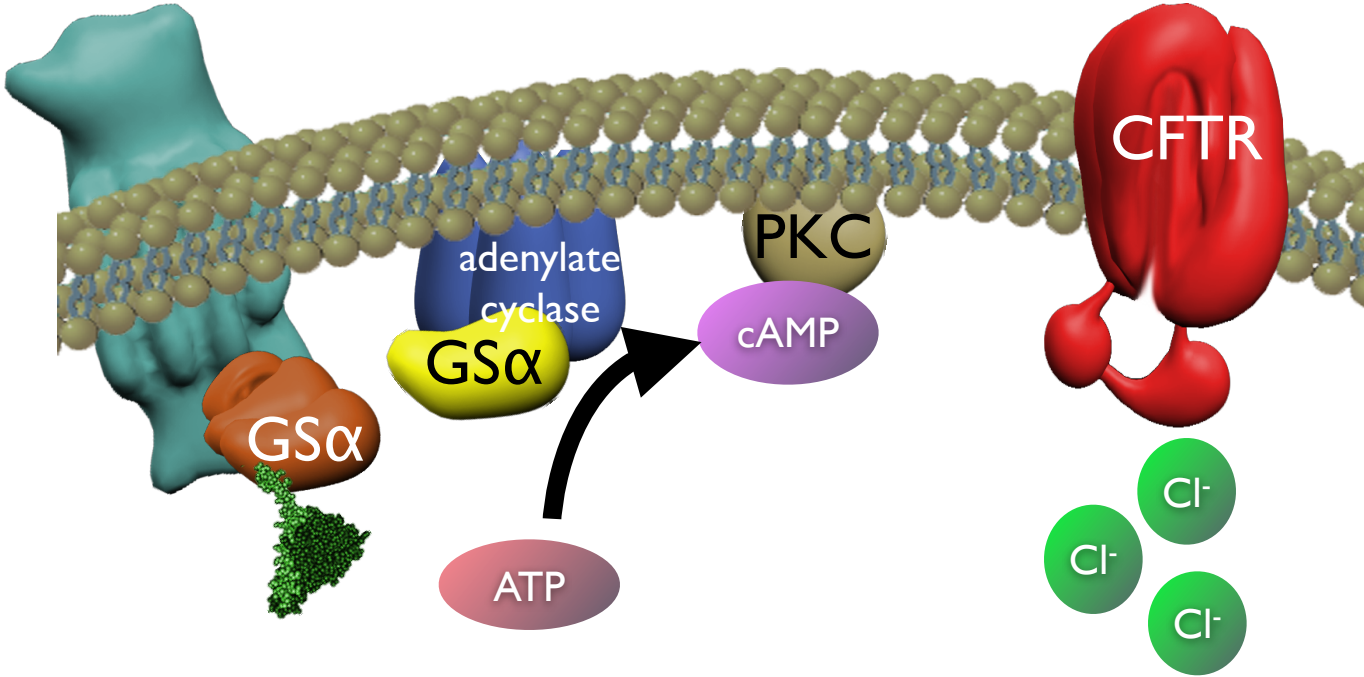

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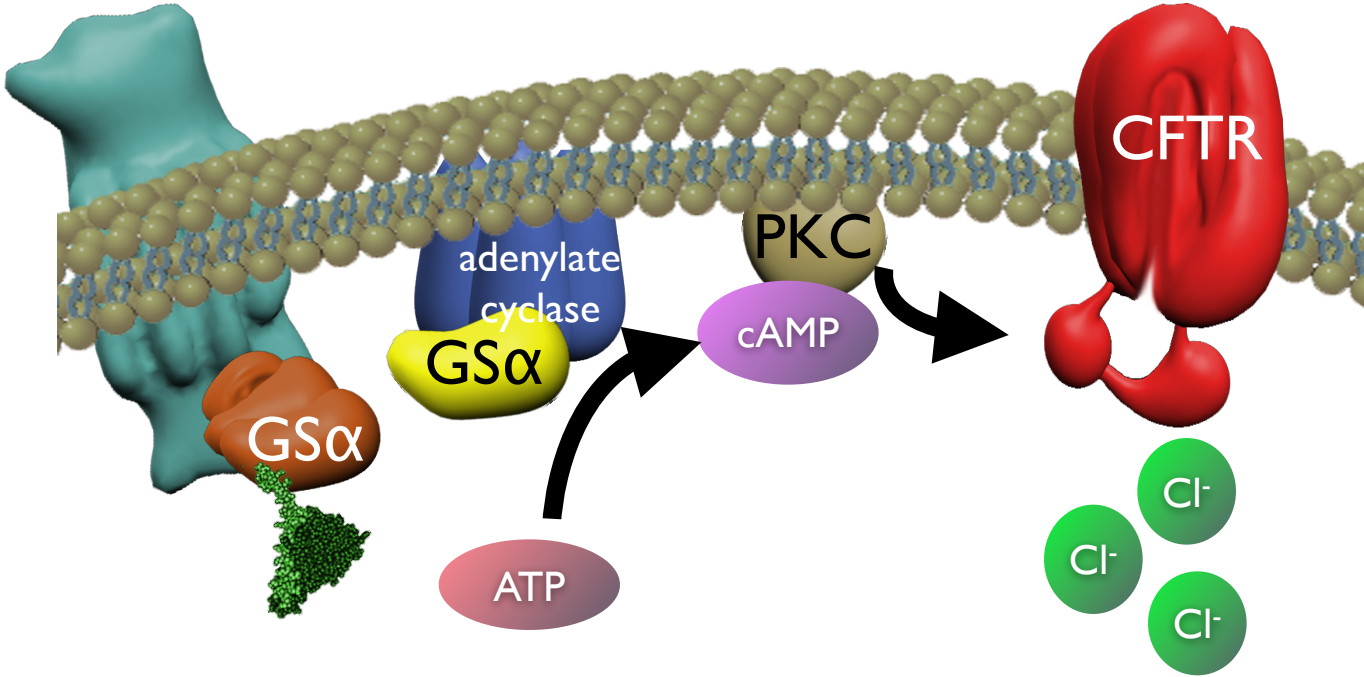

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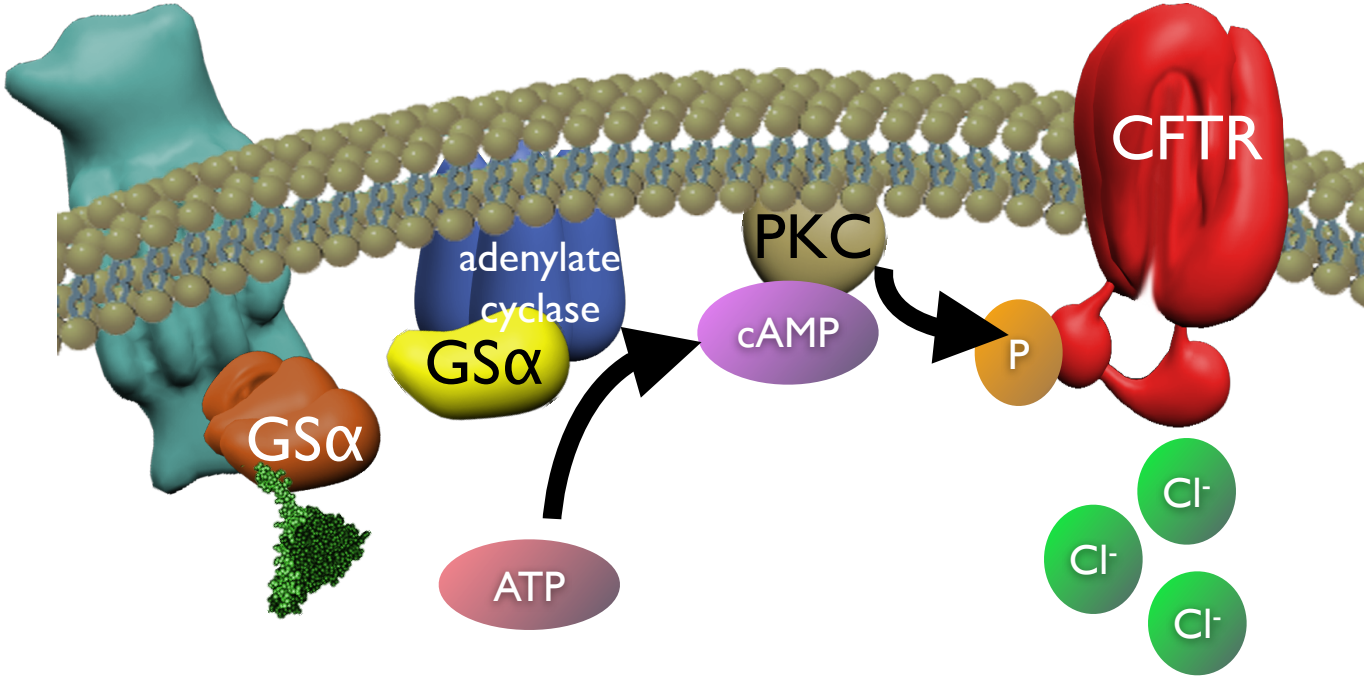

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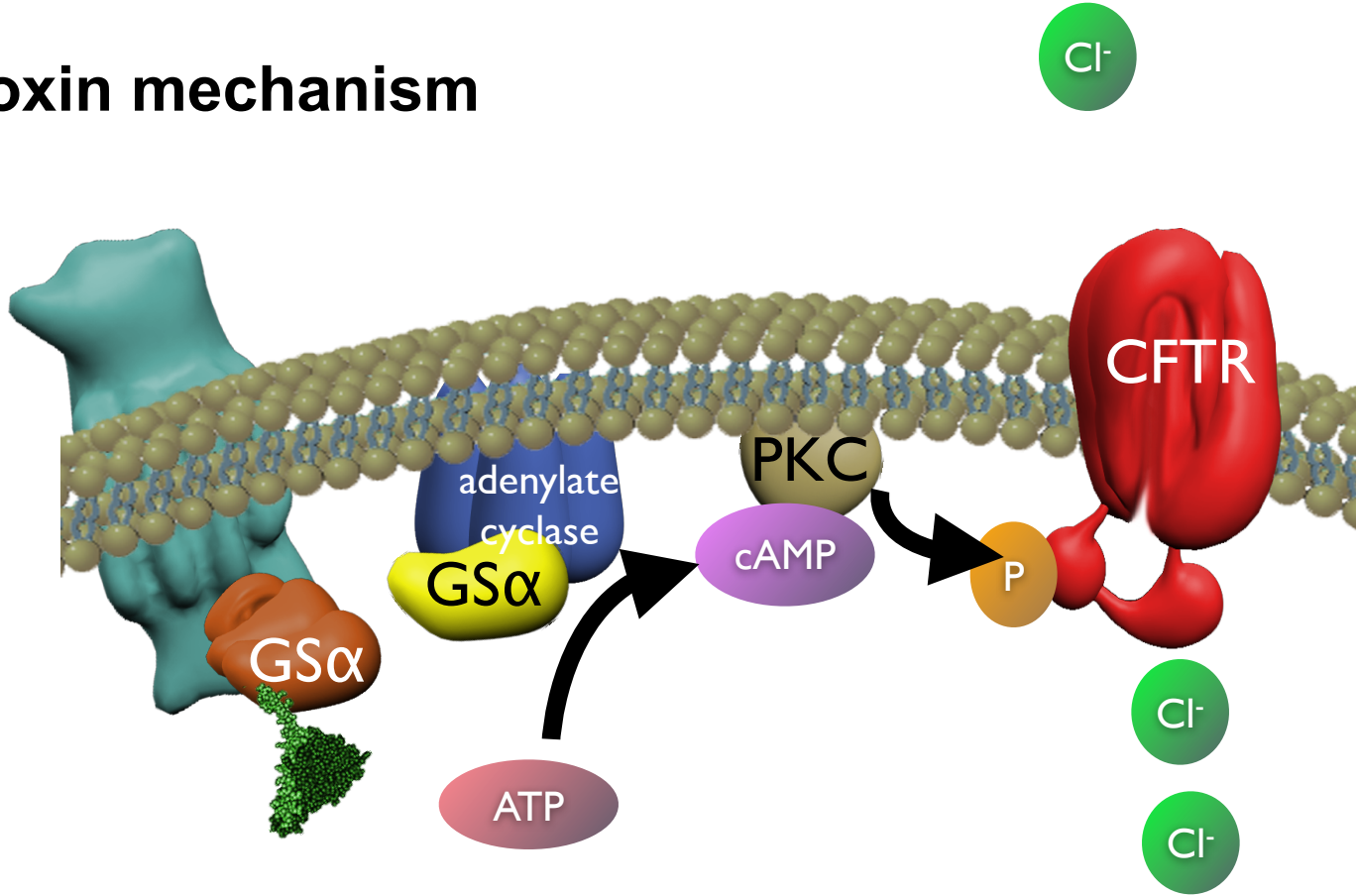

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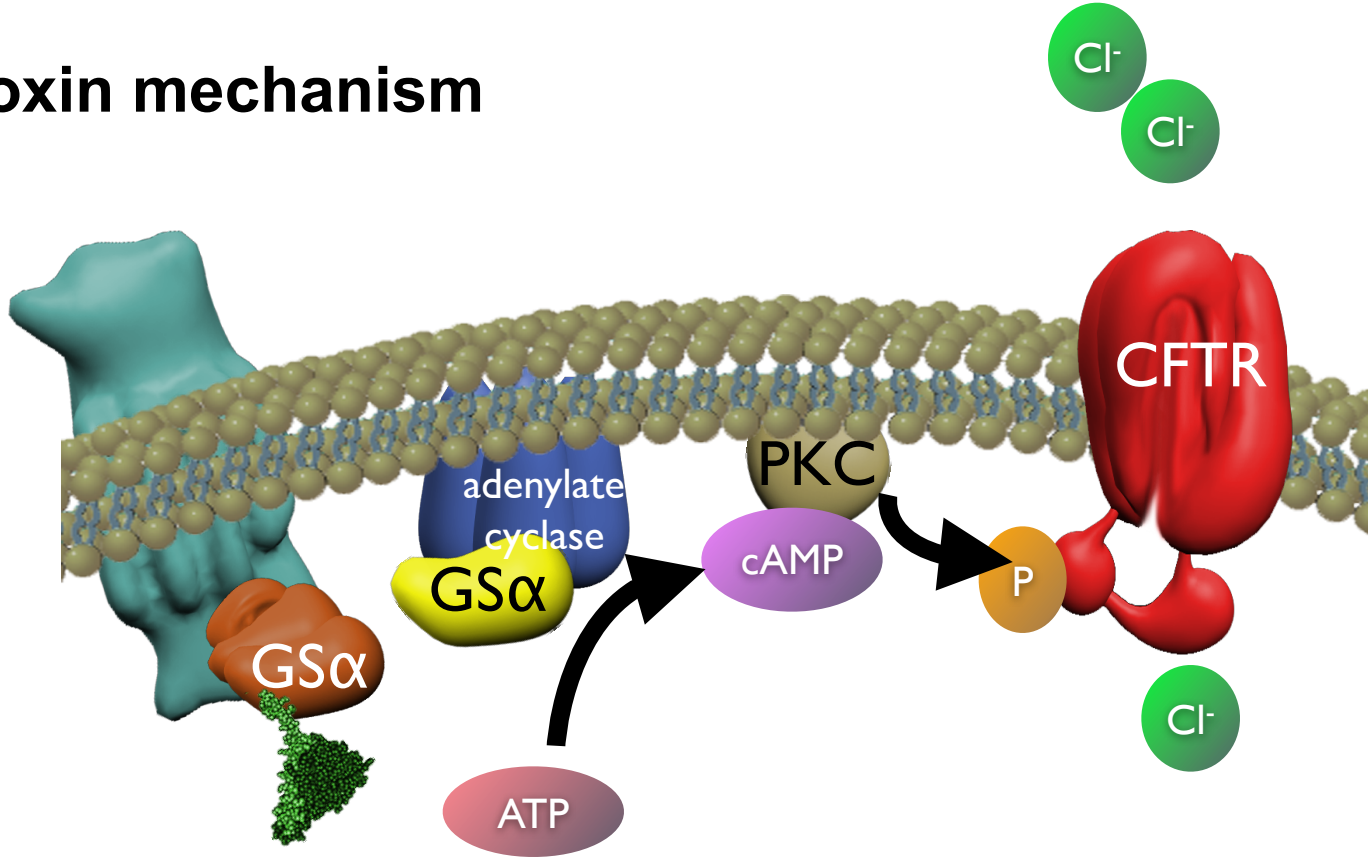

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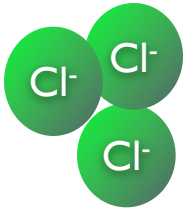

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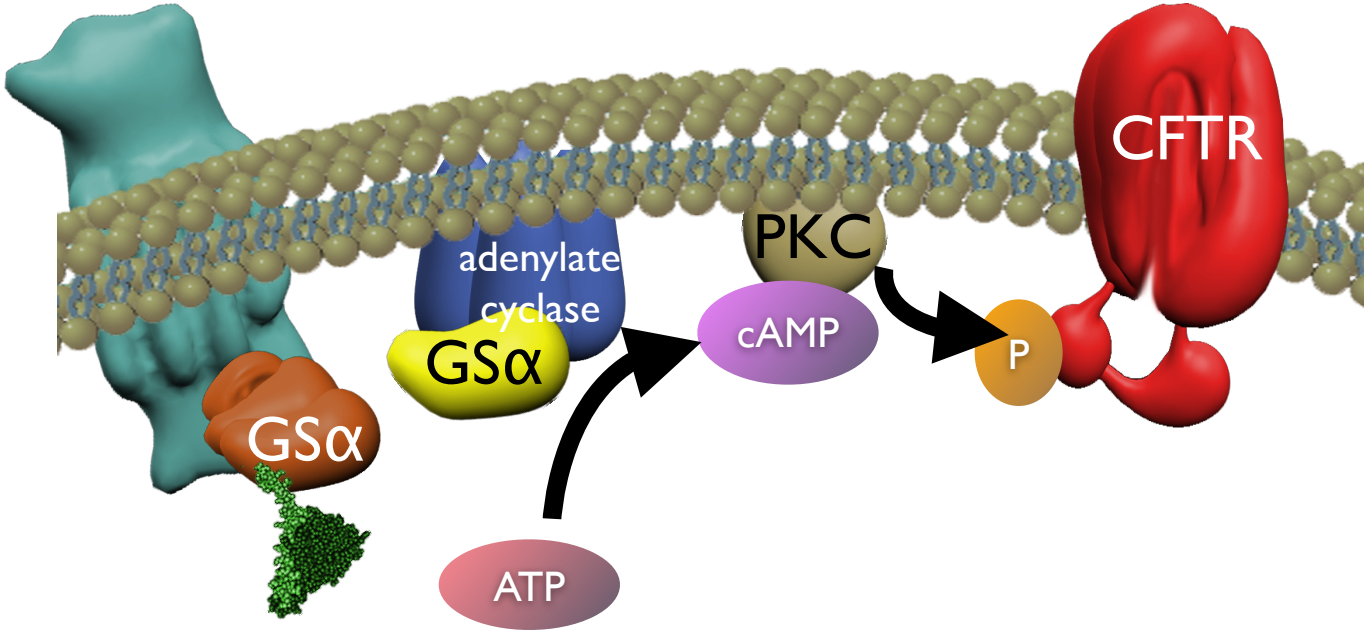

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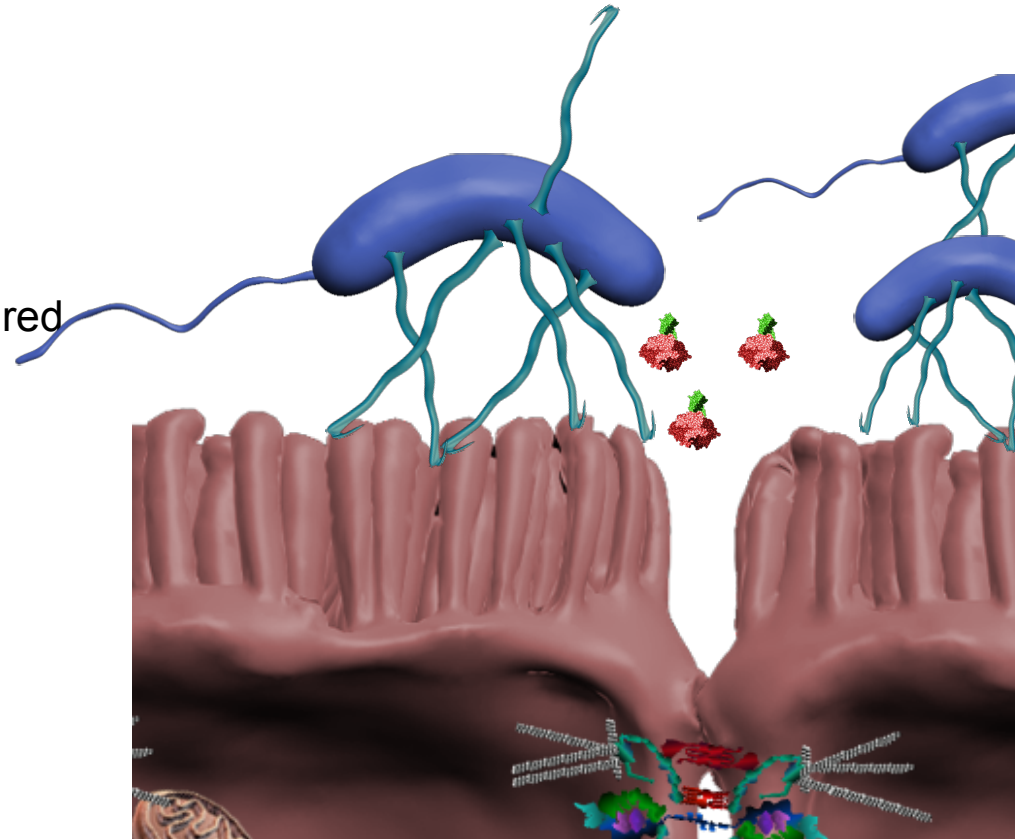

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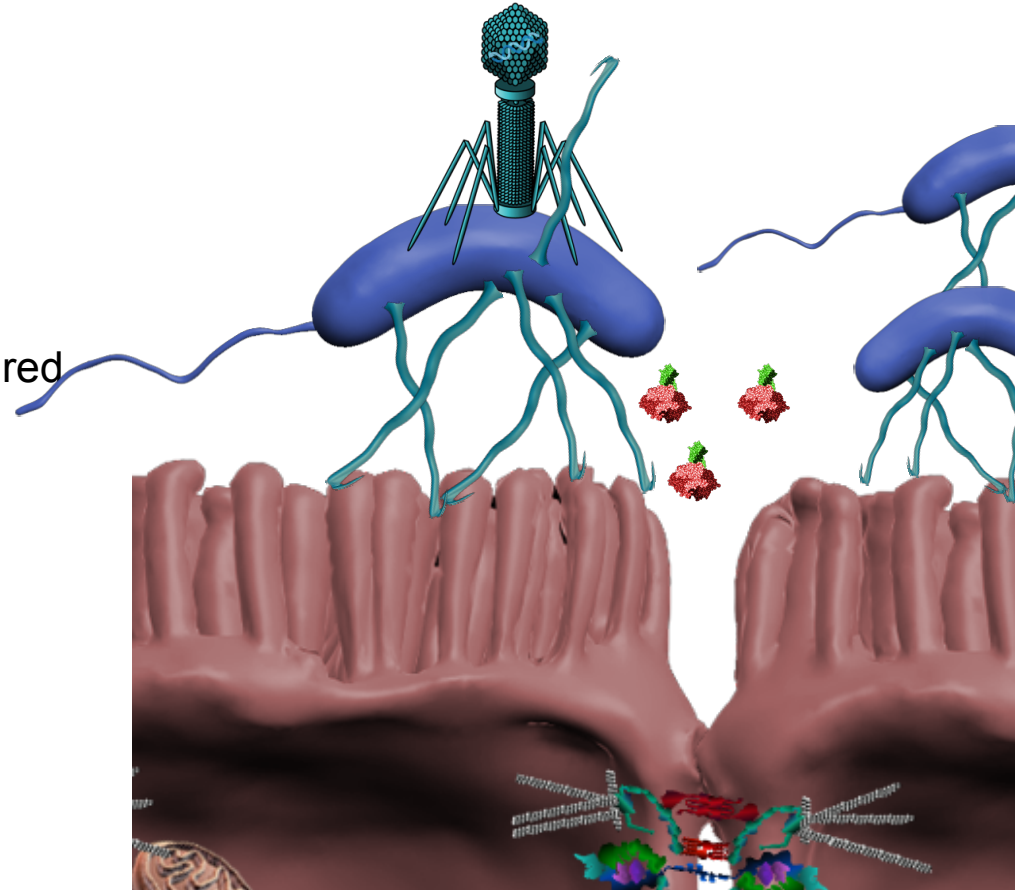

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- Main cause of travelers diarrhea
  - "Boil it, cook it, peel it, or forget it"
- Acquired virulence factors in plasmids
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- Makes two toxins that cause secretory diarrhea LT and ST

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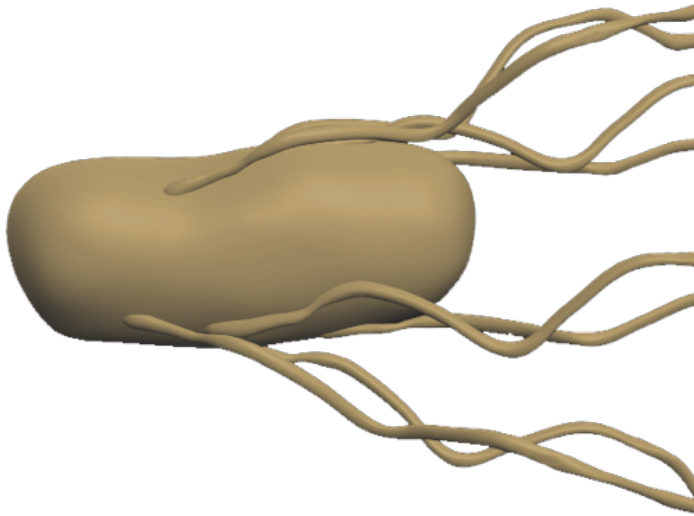

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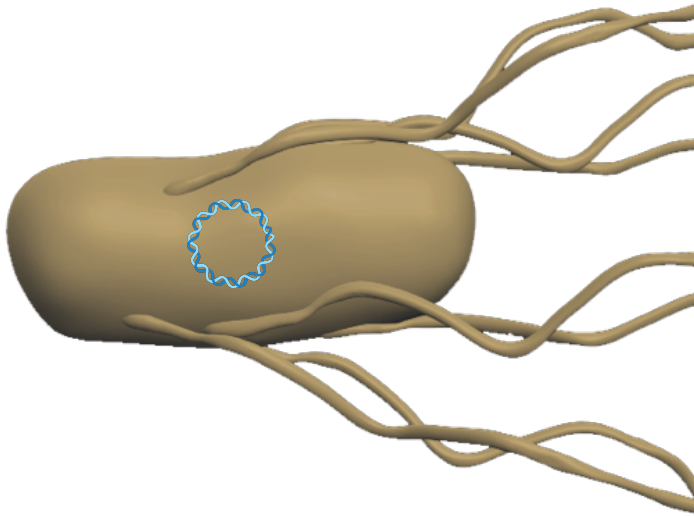

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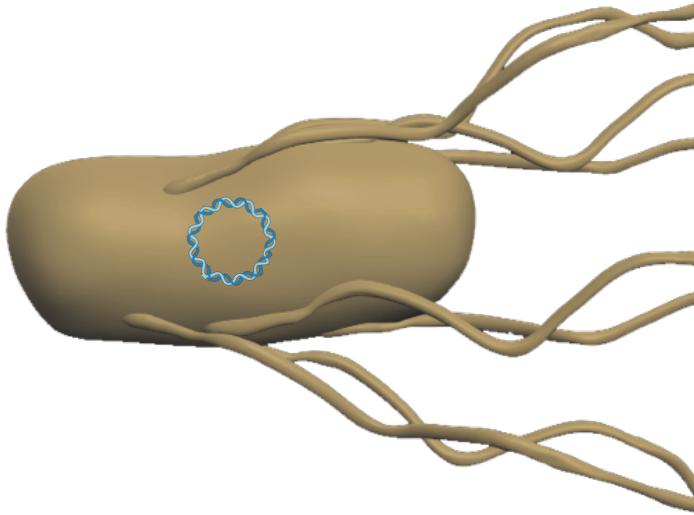

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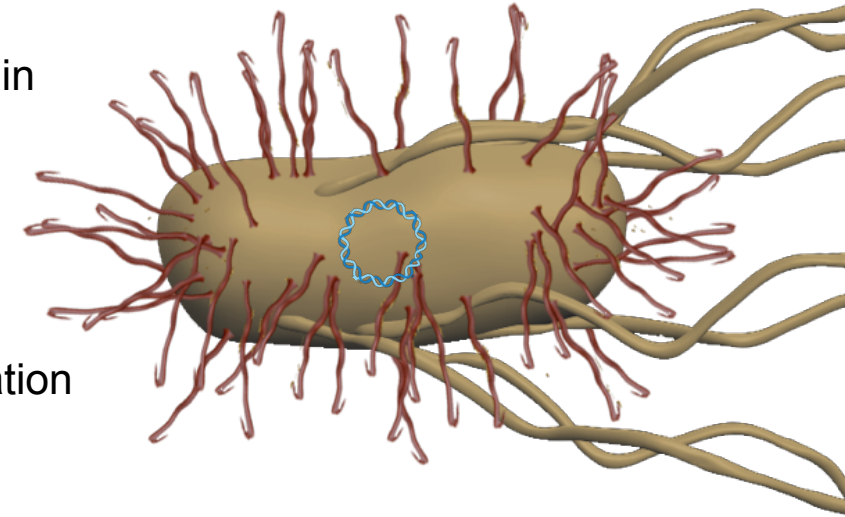
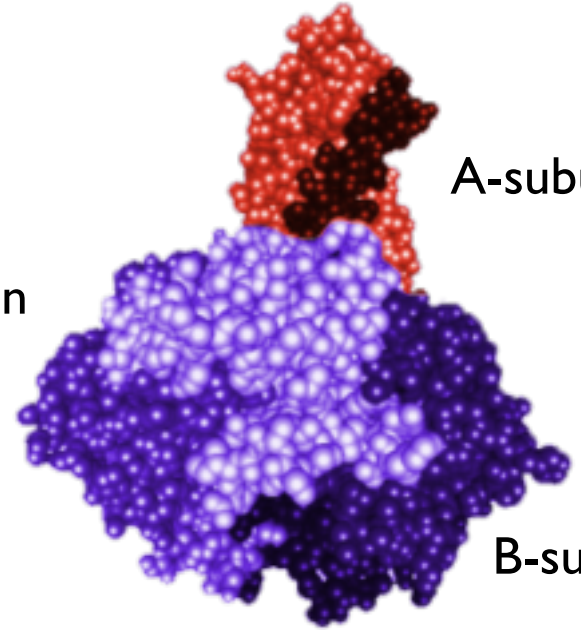


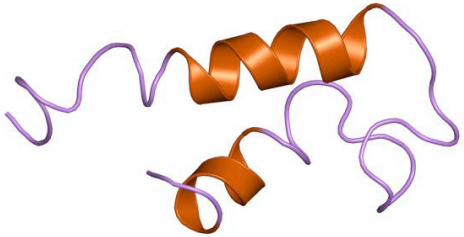
ETEC- enterotoxigenic *E. coli*

- LT- labile toxin is almost identical to cholera toxin
- ST- stable toxin are small peptides

EPEC
LT toxin



EPEC
ST toxin



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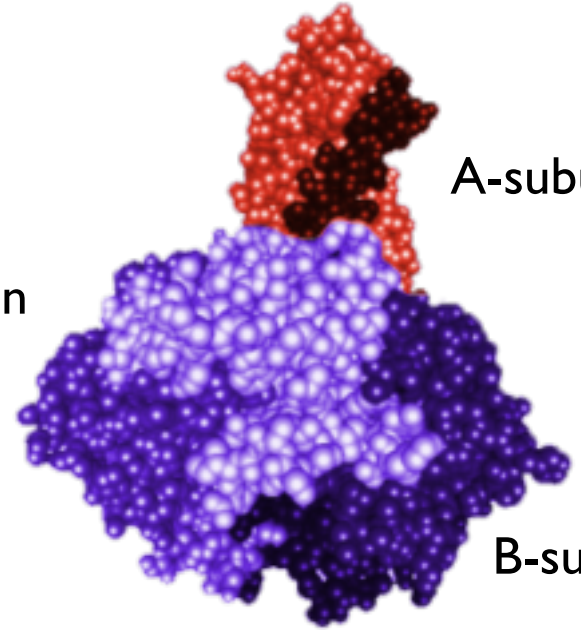
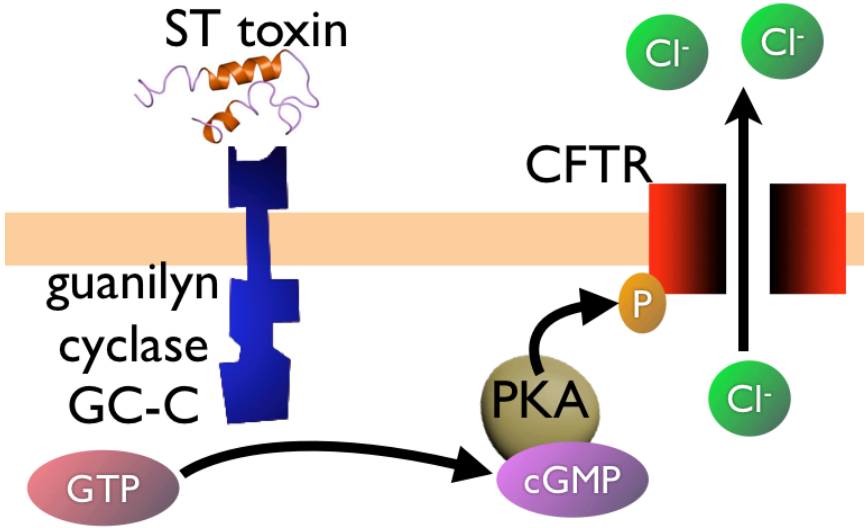
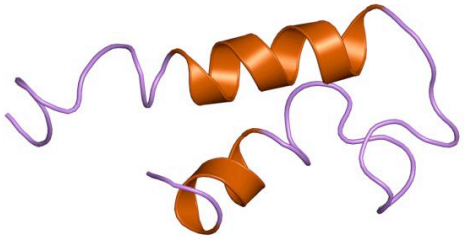
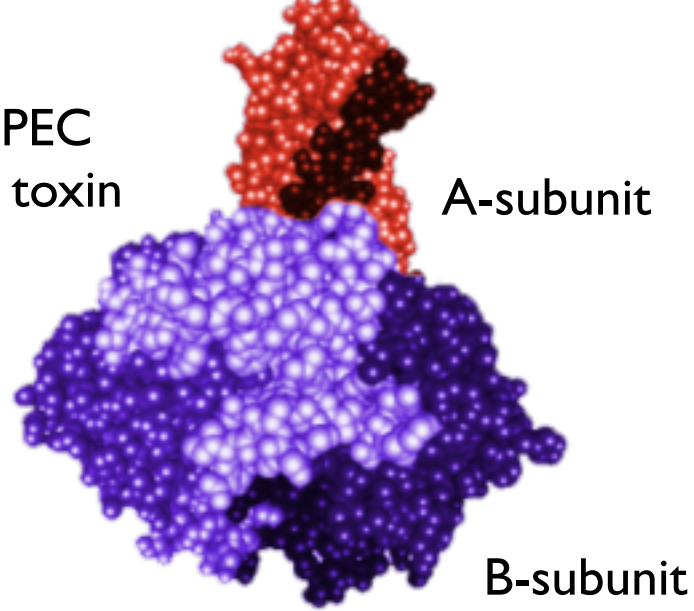




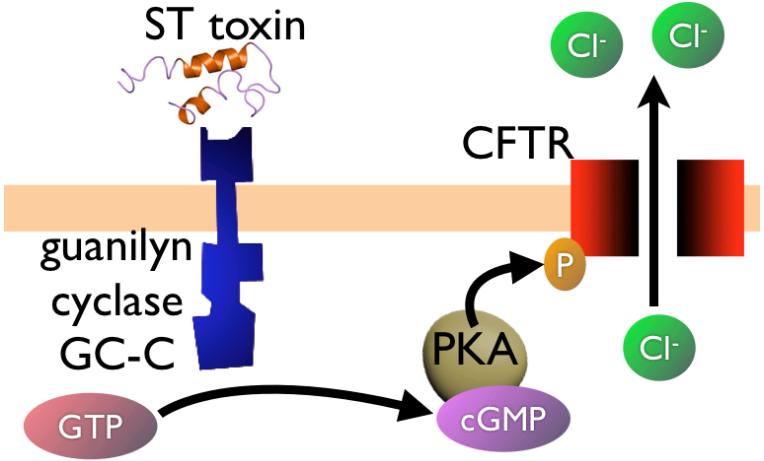
EPEC
ST toxin

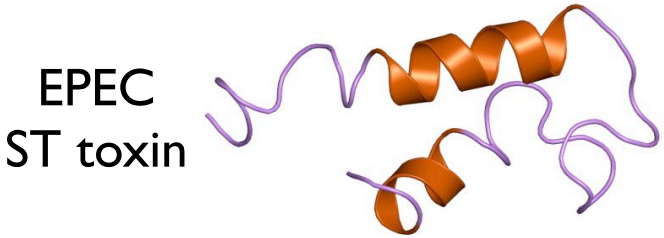


Why CFTR?



- Note that cholera toxin, LT-toxin, and ST-toxin all target the Cystic Fibrosis Transmembrane conductance regulator which controls chloride secretion
- This may be a reason mutations in CFTR are so prevalent





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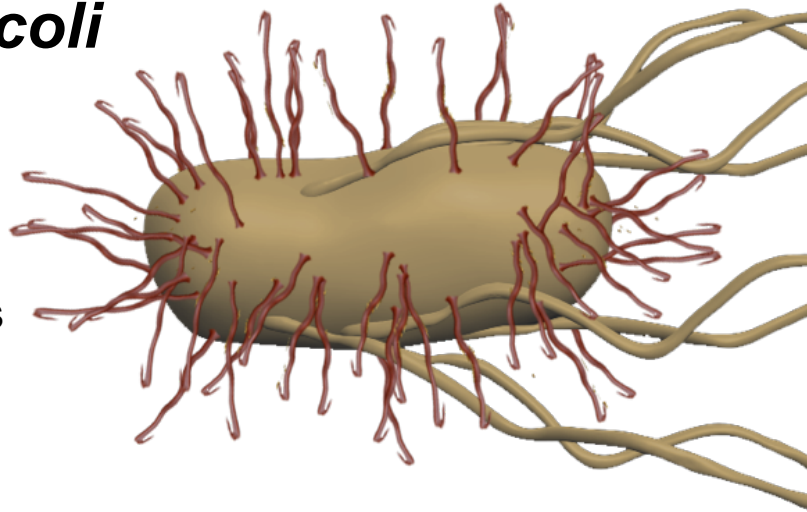

- Causes watery diarrhea of long duration mainly in infants in developing world
- Initial attachment through fimbriae (pili)- loose
- Attachment and Effacement lesions

  Pathogenicity Island (LEE locus) codes for a microinjection needle (Type 3 secretion system) used to alter adhesion to the host cell.

  - Injects its own high affinity receptor into host membrane
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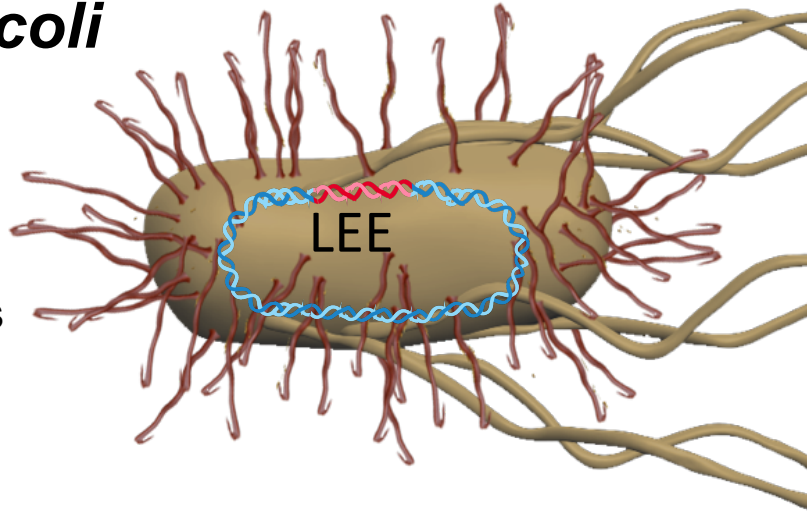

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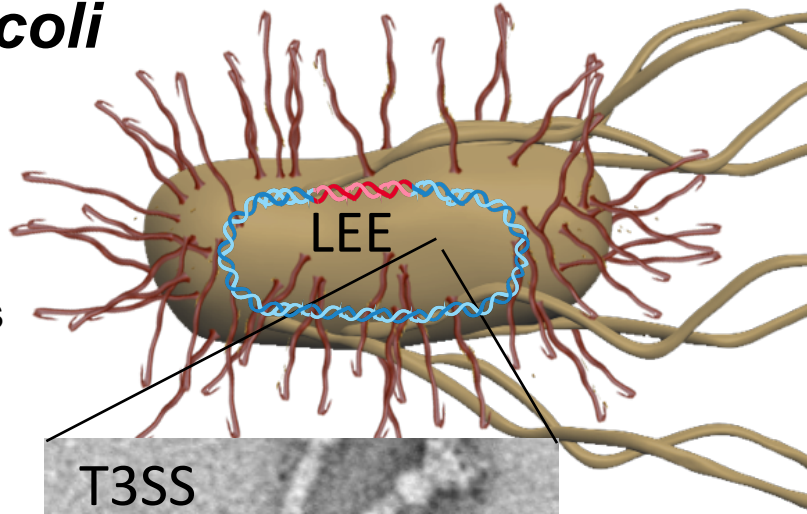

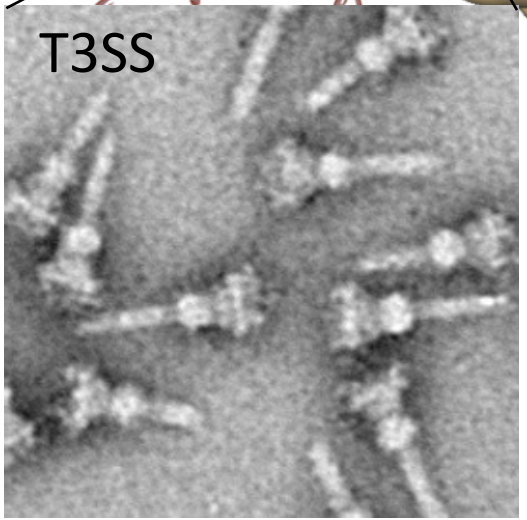

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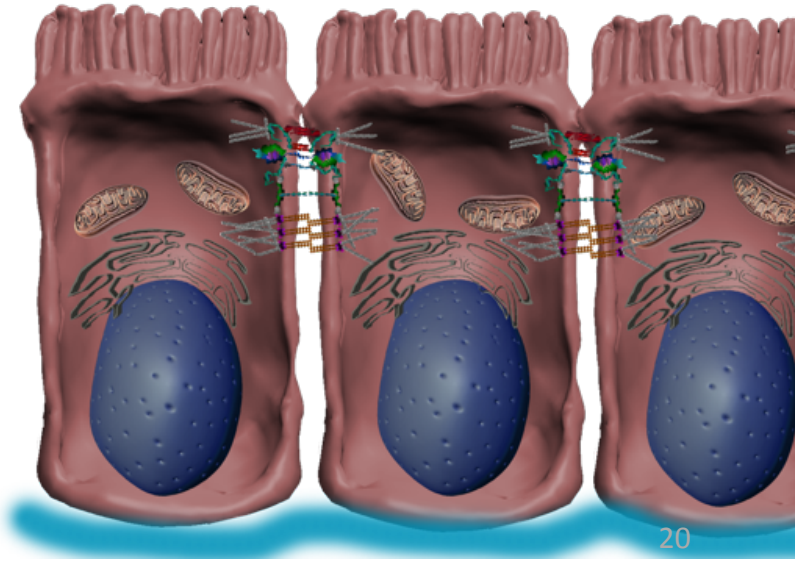

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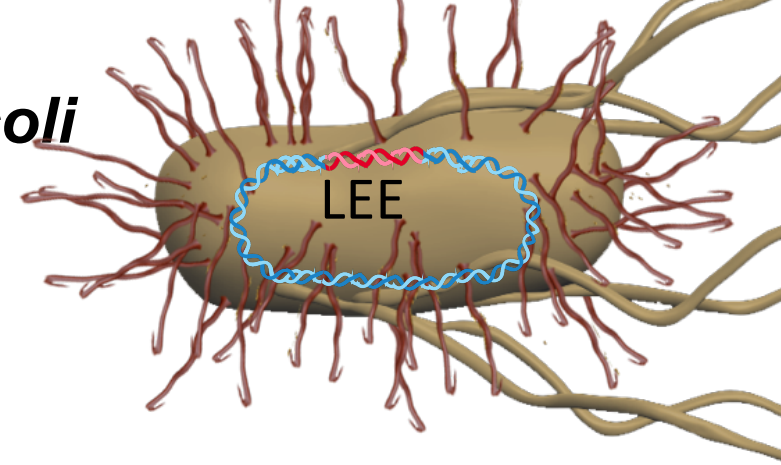

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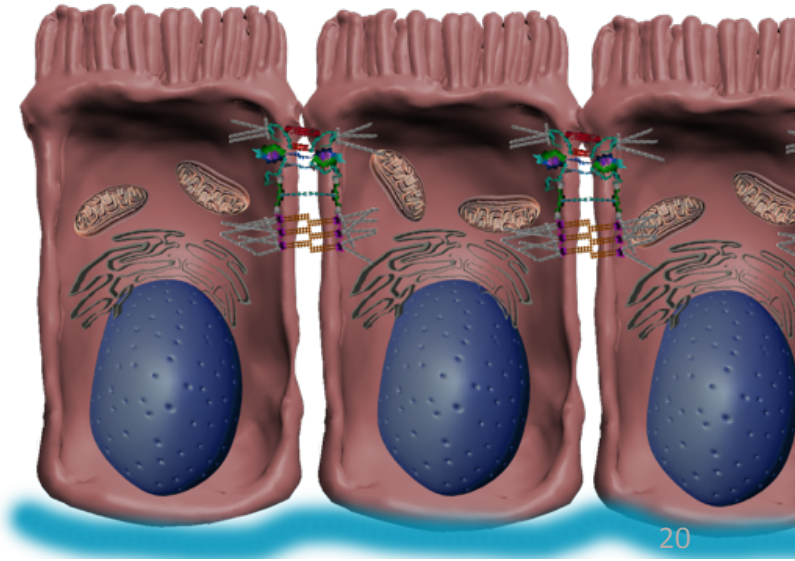

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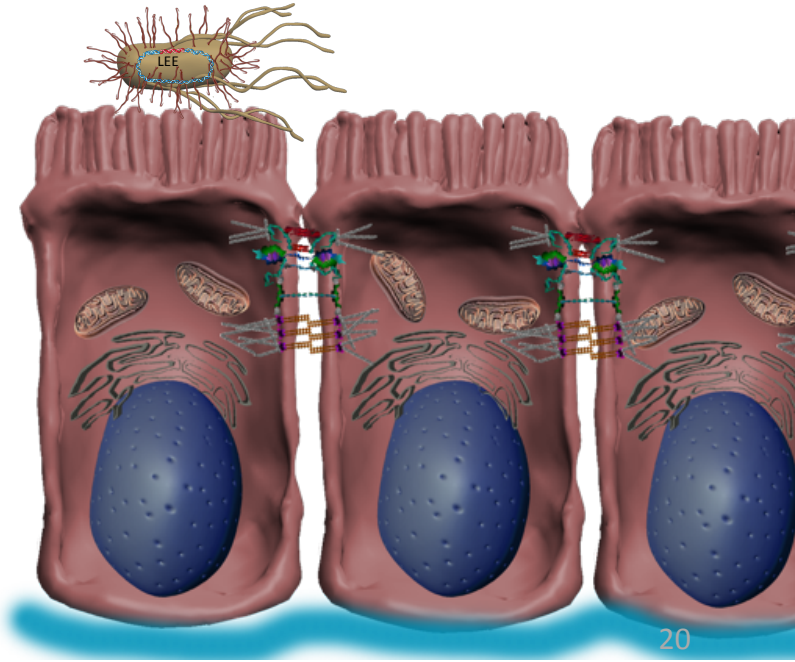

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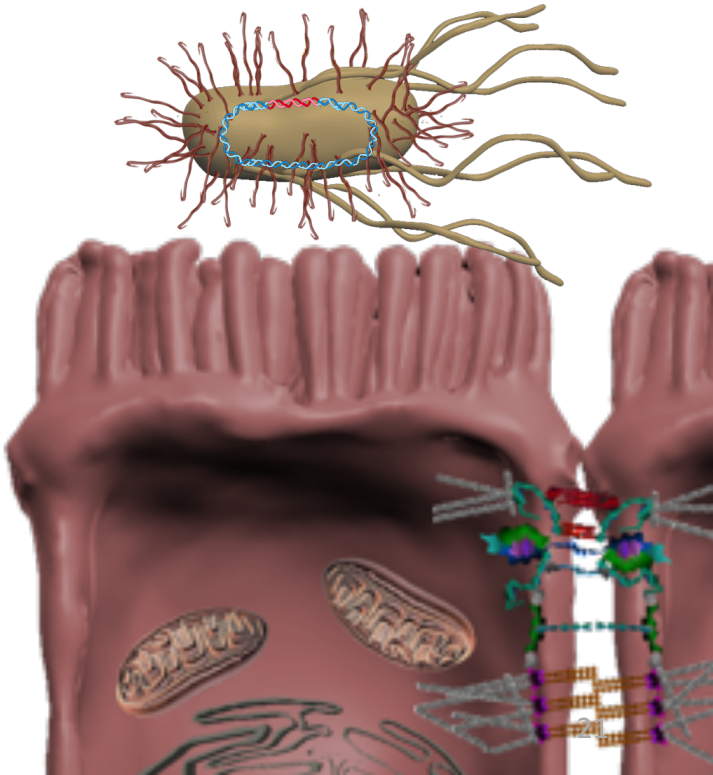

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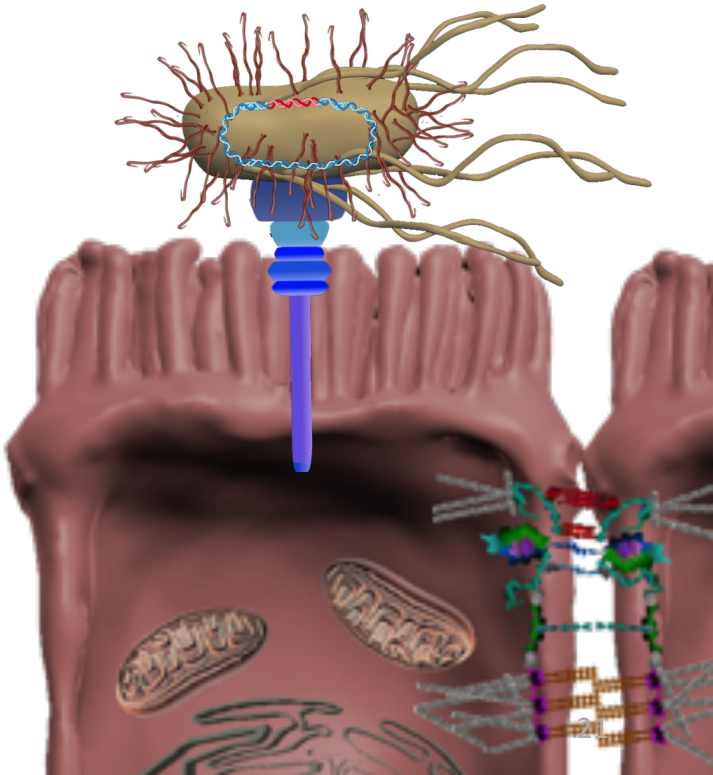

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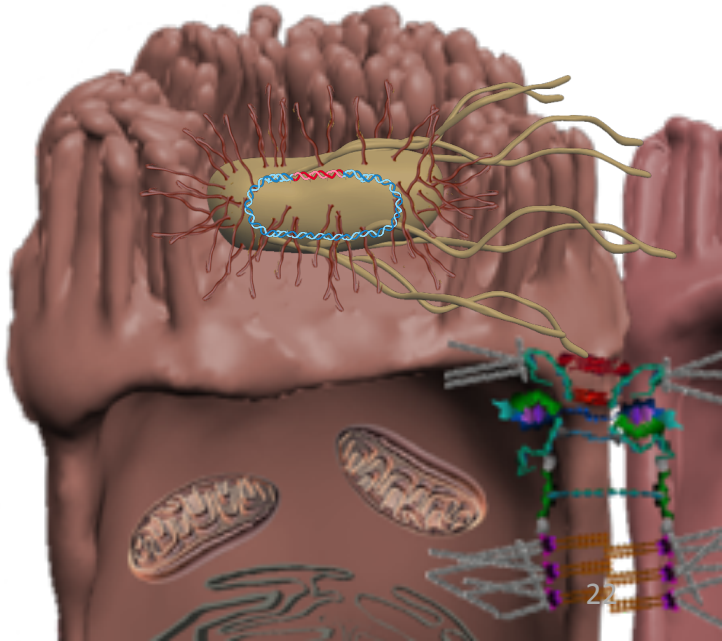

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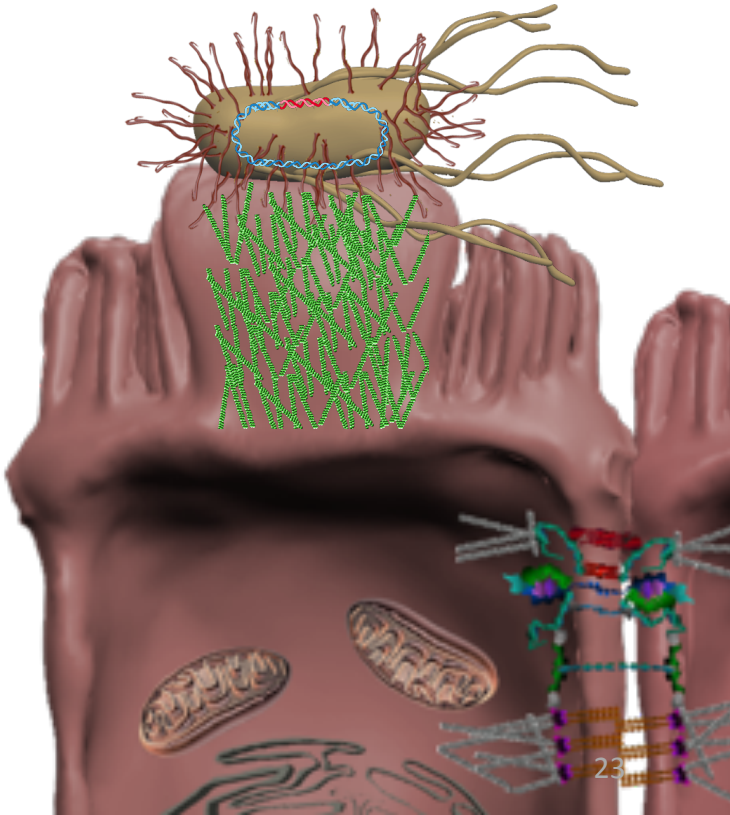

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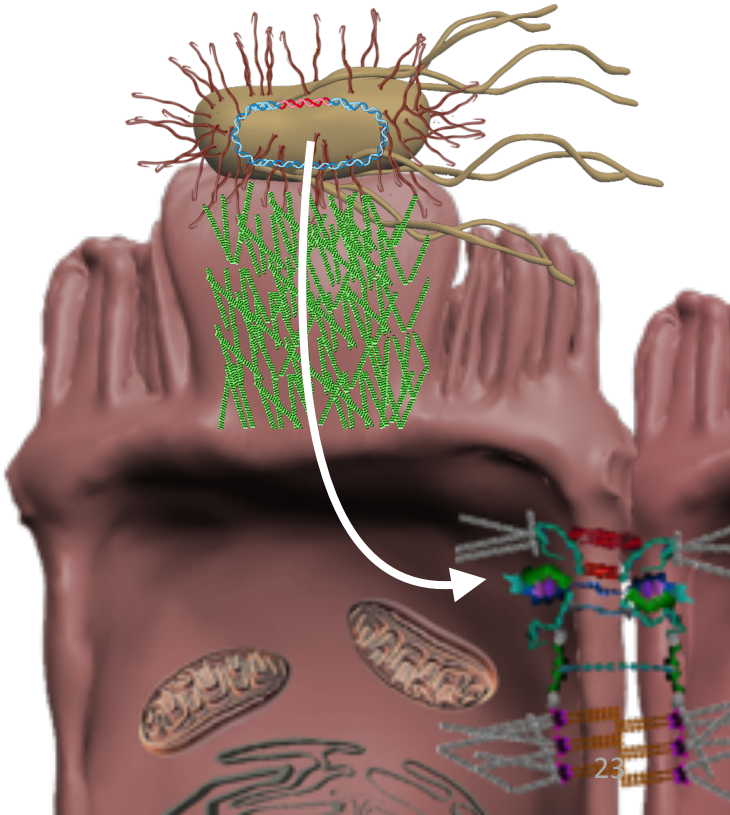

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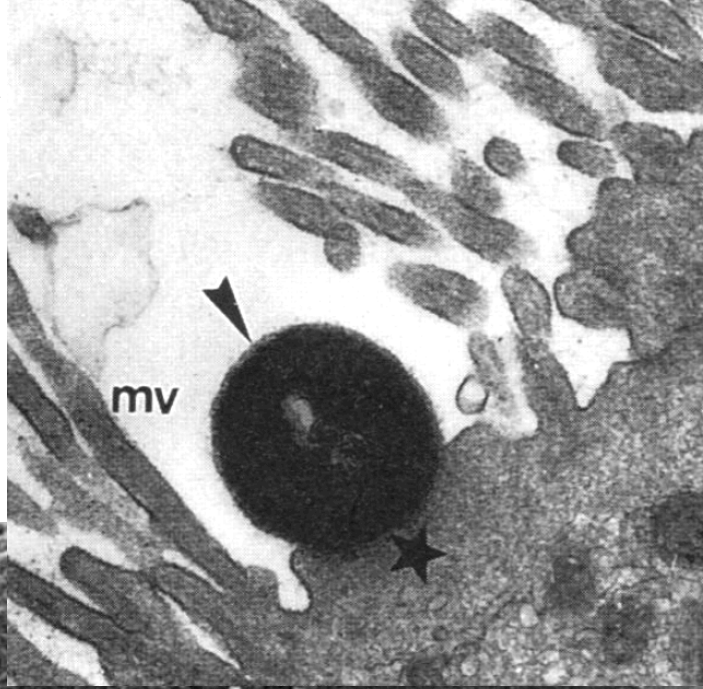

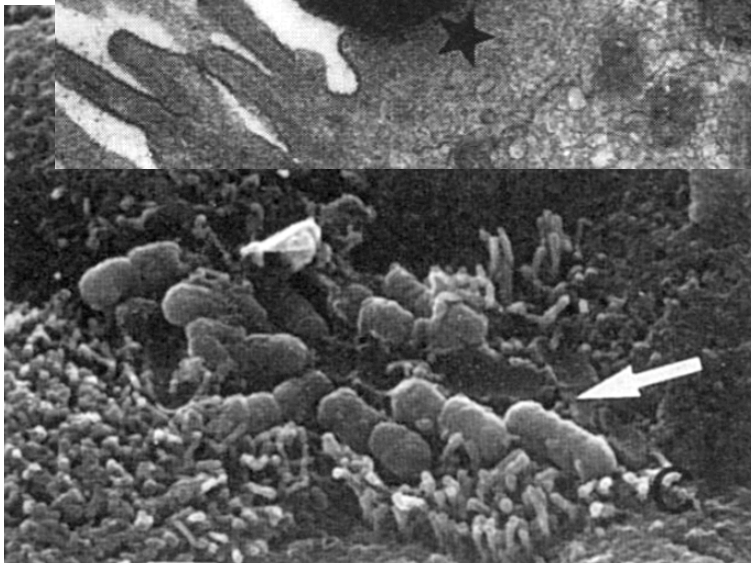

Credits: Watery Diarrhea- Bacterial Pathogens

Slide 4, 6: Rice Water Stools. From: Gastrointestinal tract infections. Mims' Medical Microbiology. Goering, Richard V., BA MSc PhD. January 1, 2013. Pages 269-302. © 2013. Figure 22.13.
https://www.clinicalkey.com

Slide 5: Severe, Acute Watery Diarrhea in an Adult. Chowdhury et al. PLoS Negl Trop Dis. Nov 2010; 4(11): e898.
Slide 19: Transmission electron-microscope image of isolated T3SS needle complexes from Salmonella typhimurium. From: Schraidt et al. (2010), Topology and Organization of the Salmonella typhimurium Type III Secretion Needle Complex Components. PLoS Pathog 6(4): e1000824. doi:10.1371/journal.ppat.1000824
http://commons.wikimedia.org/wiki/File:TEM_of_isolated_T3SS_needle_complexes.jpg

Slide 24: TEM of an EPEC forming an attachment and effacement lesion. From: Pedrozo et al. Attaching-Effacing Lesions and Intracellular Penetration in HeLa Cells and Human Duodenal Mucosa by Two Escherichia coli Strains Not Belonging to the Classical Enteropathogenic E. coli Serogroups. Infection and Immunity Mar 1993 p 1152-56