

## Selective depletion of uropathogenic *E. coli* from the gut by a FimH antagonist

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A spoonful of sugar could be the medicine to treat pathogenic bacteria.

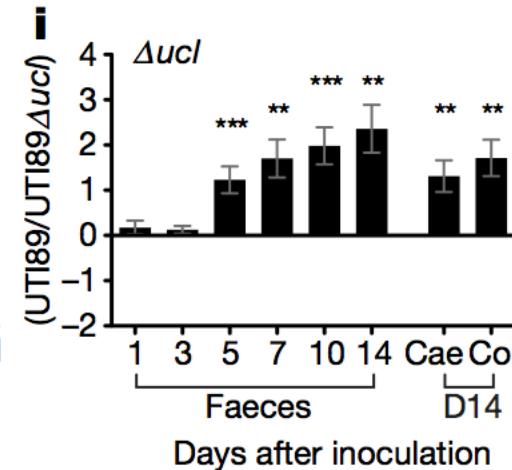
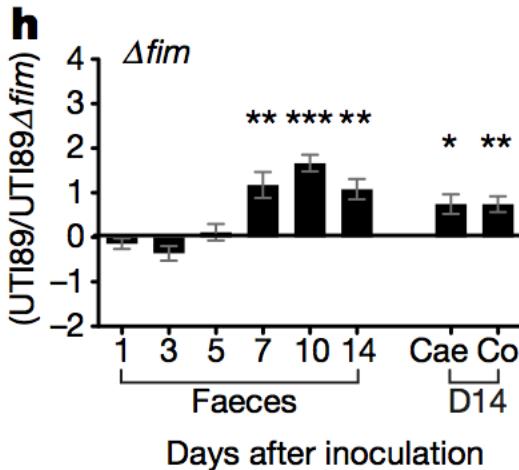
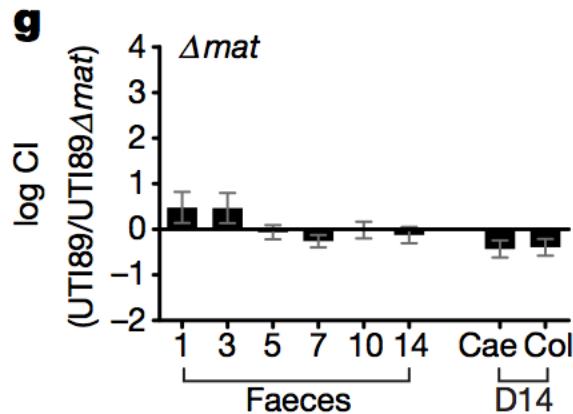
# UTI is caused by pathogenic *E. coli* with pili

- Urinary tract infection (UTI) caused by uropathogenic *E. coli* (UPEC) affects 150 million people annually. Antibiotic resistance exacerbates recurrent UTIs.
- UPEC is a commensal in the gut but pathogenic in the bladder.
- UPEC residing in the gut are shed in the feces and colonize the peri-urethral and vaginal areas before ascending into the bladder.
- Previous studies have demonstrated an essential role for **pili** in host–UPEC interactions at sites of infection such as the bladder and kidneys.
- A type of pilus called the chaperone-usher pathway (**CUP**) pilus is widespread in bacteria, including UPEC.

Hypothesis 1: CUP pili are gut colonization determinants

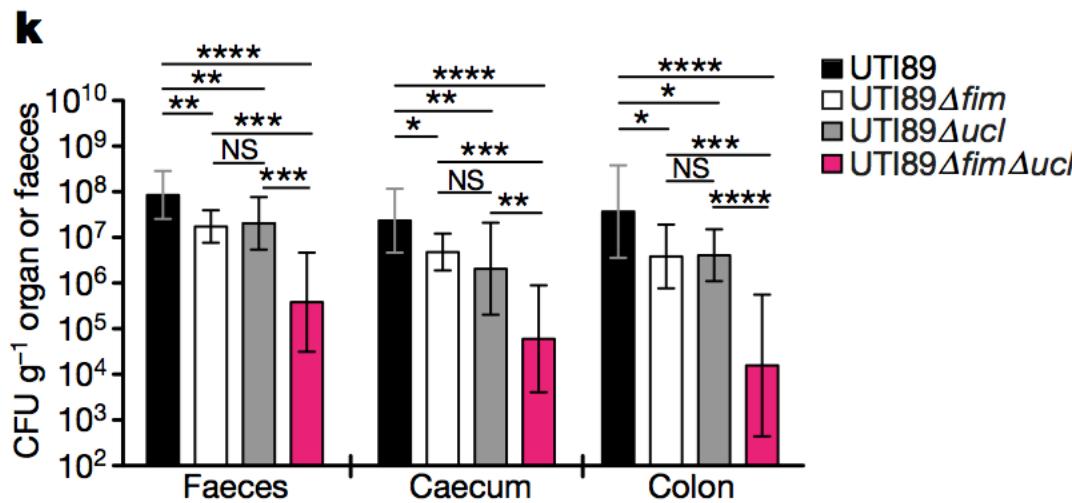
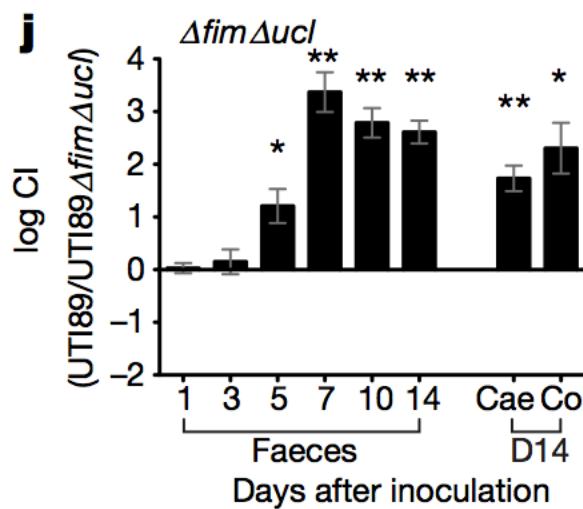
Hypothesis 2: Targeting the CUP pili might be a treatment to UTI

# Type I and F-17 like pili promote UPEC gut colonization

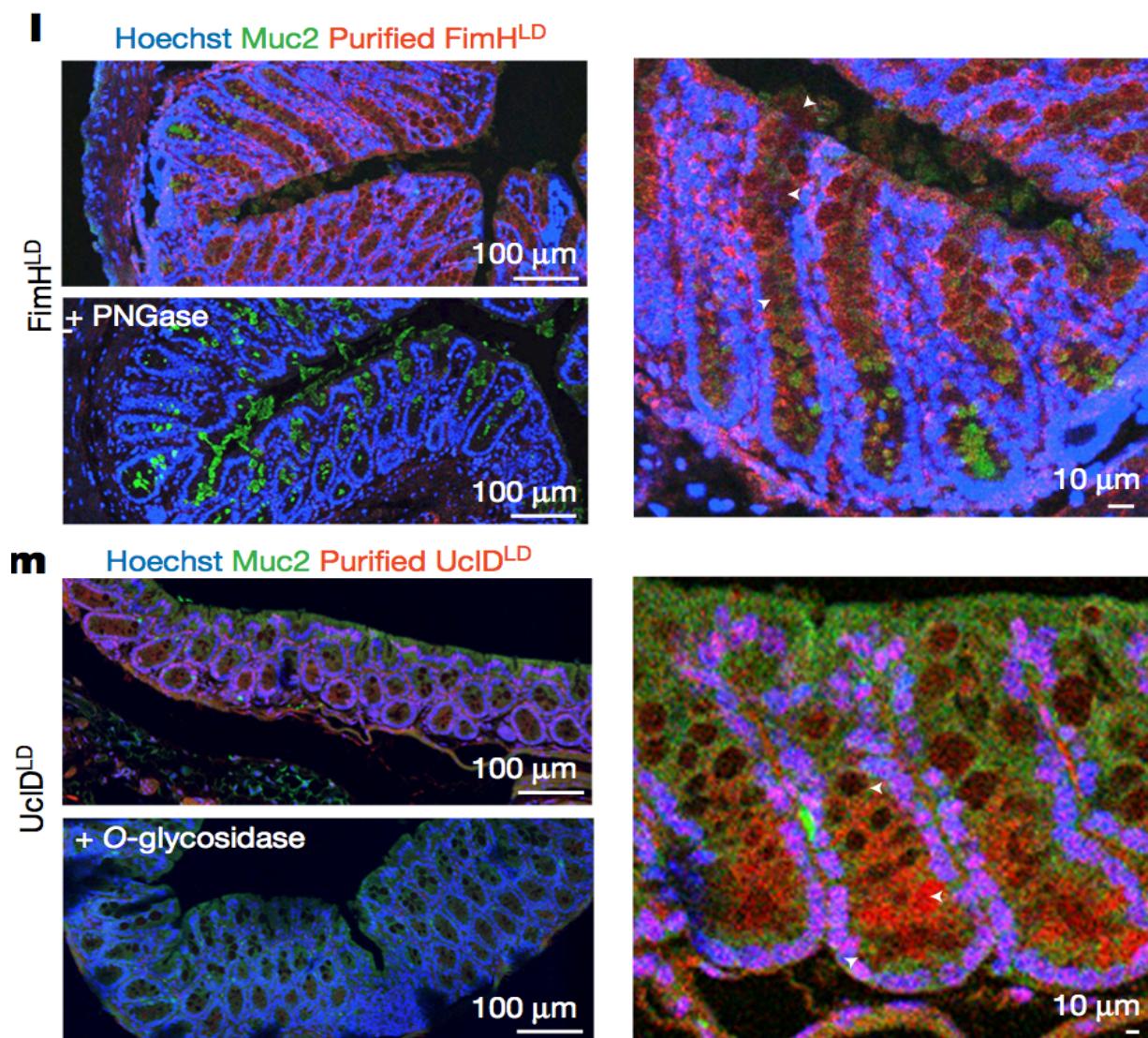


*ucl*: F17-like pili

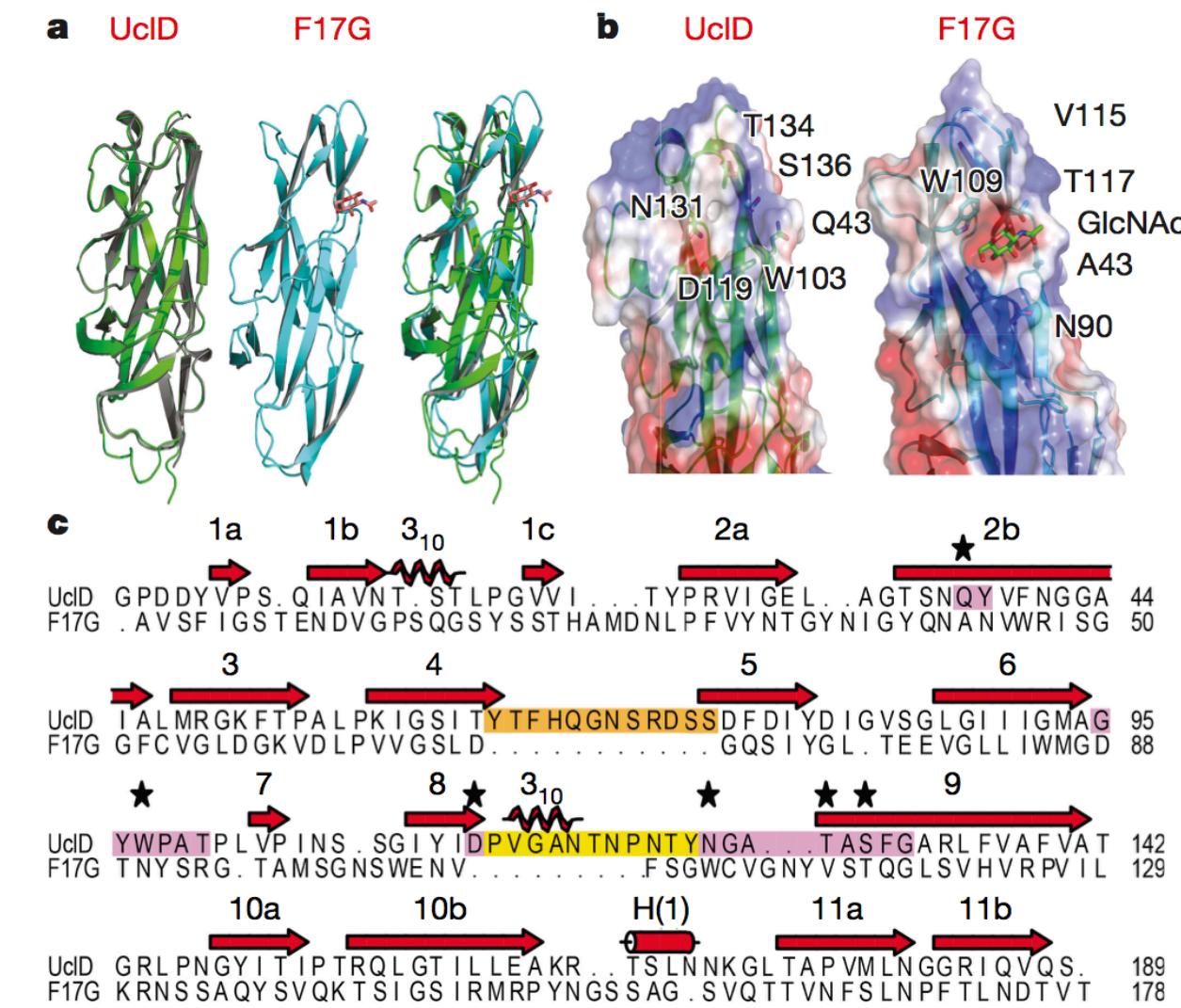
*fim*: Type I pili



Type 1 adhesins bind to  
'N-linked' glycans  
(e.g.) sugar D-mannose,  
while F-17 binds to 'O-  
linked' glycans



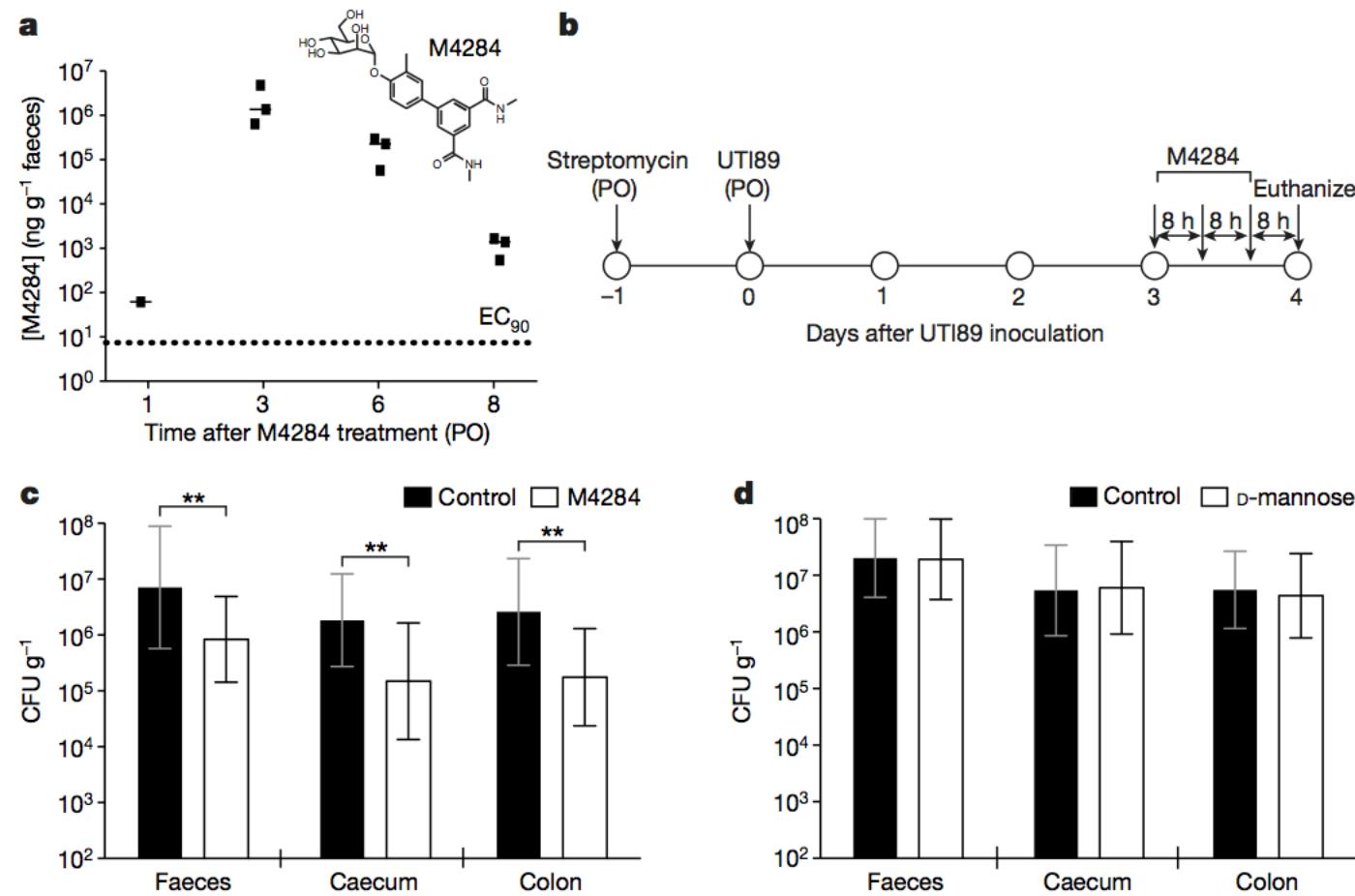
# Structural differences further suggest different bindings



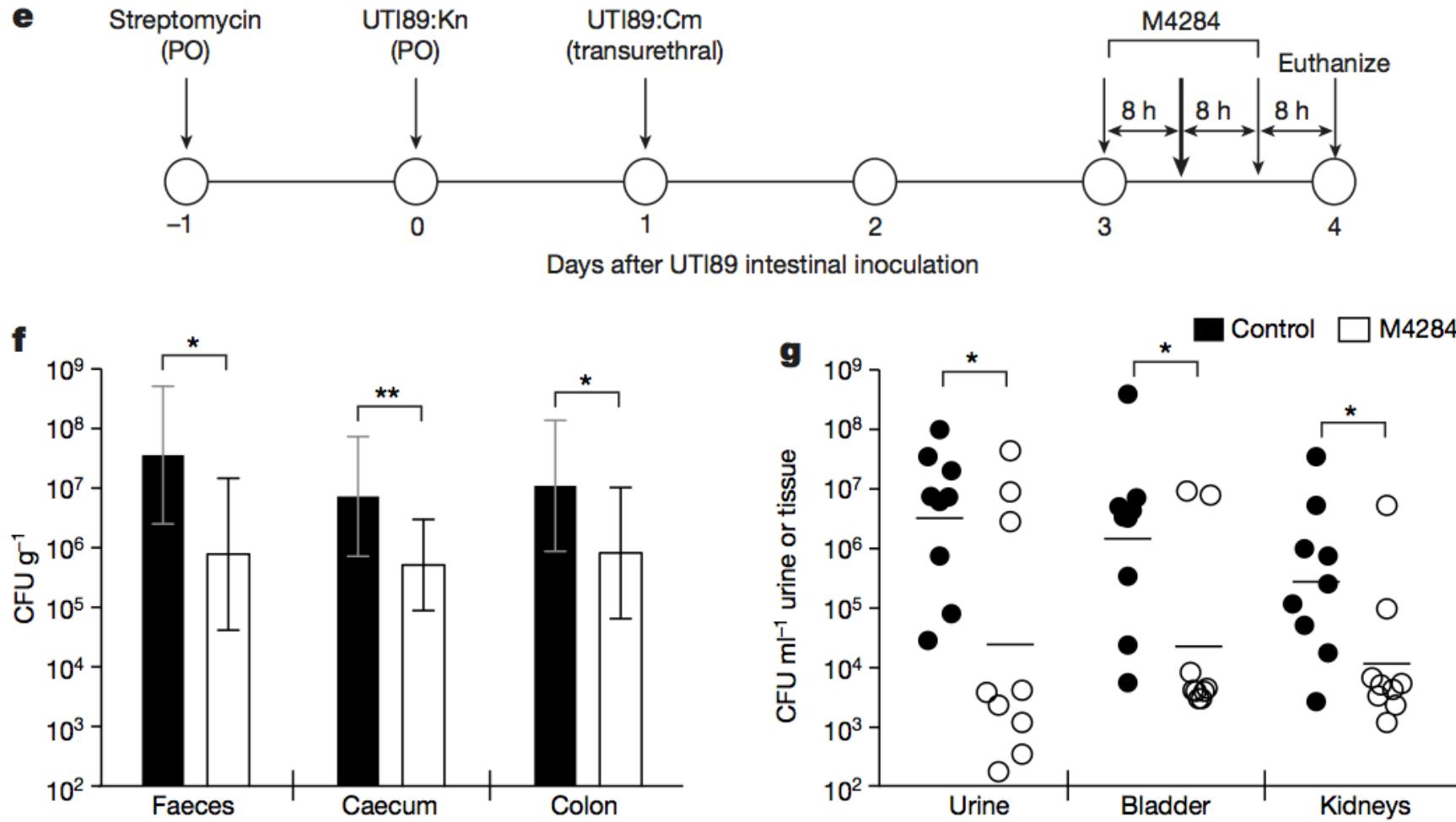
Hypothesis 1: CUP pili is a gut colonization determinant

Hypothesis 2: Targeting the CUP pili might be a treatment to UTI

# Compound M4284, a mannoside, reduces the UPEC intestinal reservoir



# M4284 simultaneously treats UTI???



- Decrease the dose of PUEC introduced into the bladder from  $10^8$  to  $10^6$  significantly reduced the rate of UTI.
- Mechanism of reducing bladder UPEC is unclear.

# M4284 simultaneously treats UTI...

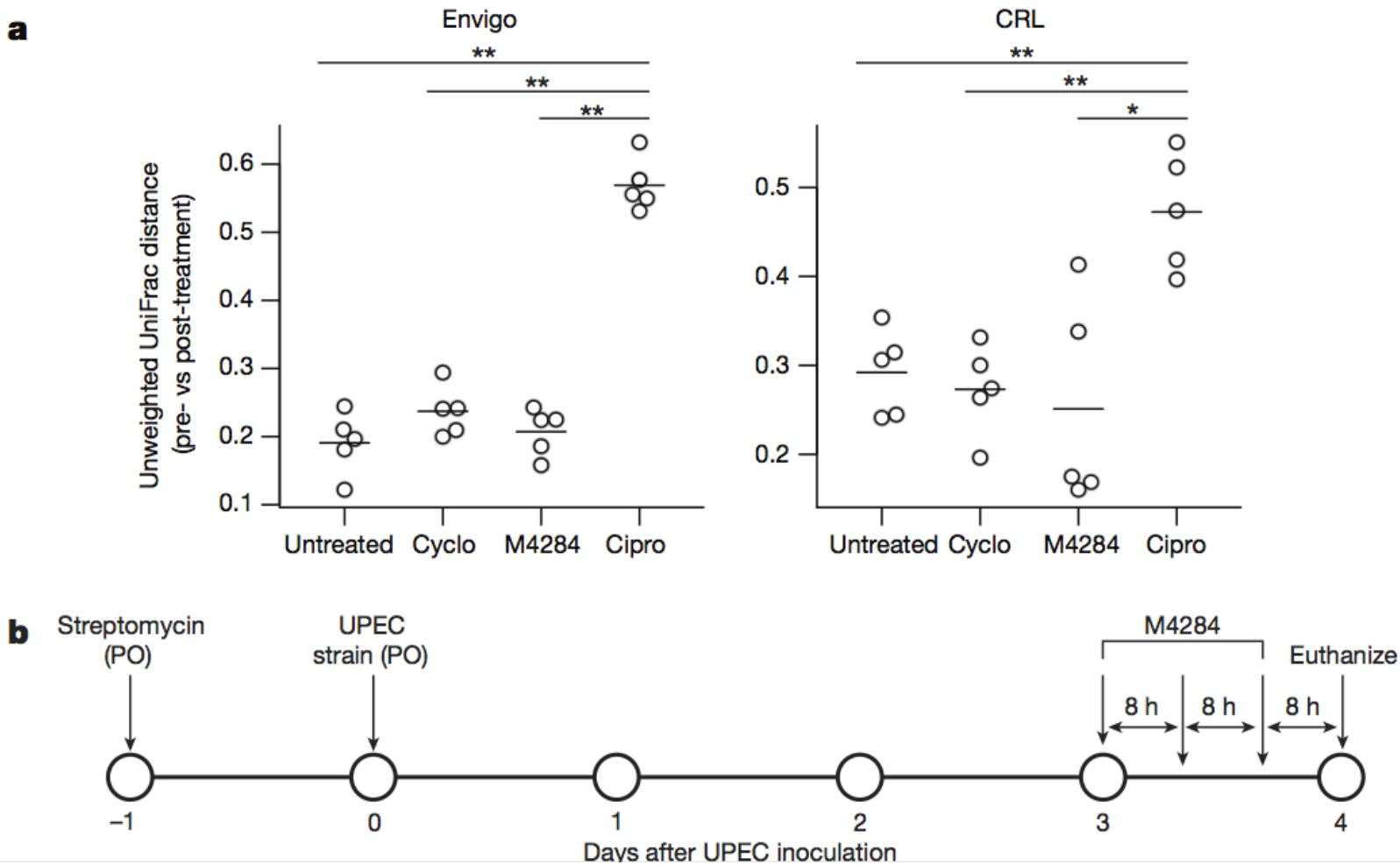
## URINARY TRACT INFECTION

### Treatment and Prevention of Urinary Tract Infection with Orally Active FimH Inhibitors 2011

Corinne K. Cusumano,<sup>1,2</sup> Jerome S. Pinkner,<sup>1,2</sup> Zhenfu Han,<sup>3</sup> Sarah E. Greene,<sup>1,2</sup> Bradley A. Ford,<sup>2,4</sup> Jan R. Crowley,<sup>5</sup> Jeffrey P. Henderson,<sup>2,5</sup> James W. Janetka,<sup>3,\*</sup> Scott J. Hultgren<sup>1,2,\*</sup>

Chronic and recurrent urinary tract infections pose a serious medical problem because there are few effective treatment options. Patients with chronic urinary tract infections are commonly treated with long-term prophylactic antibiotics that promote the development of antibiotic-resistant forms of uropathogenic *Escherichia coli* (UPEC), further complicating treatment. We developed small-molecular weight compounds termed mannosides that specifically inhibit the FimH type 1 pilus lectin of UPEC, which mediates bacterial colonization, invasion, and formation of recalcitrant intracellular bacterial communities in the bladder epithelium. Here, we optimized these compounds for oral bioavailability and demonstrated their fast-acting efficacy in treating chronic urinary tract infections in a preclinical murine model. These compounds also prevented infection *in vivo* when given prophylactically and strongly potentiated the activity of the current standard of care therapy, trimethoprim-sulfamethoxazole, against clinically resistant PBC-1 UPEC bacteria. These compounds have therapeutic efficacy after oral administration for the treatment of established urinary tract infections *in vivo*. Their unique mechanism of action—targeting the pilus tip adhesin FimH—circumvents the conventional requirement for drug penetration of the outer membrane, minimizing the potential for the development of resistance. The small-molecular weight compounds described herein promise to provide substantial benefit to women suffering from chronic and recurrent urinary tract infections.

# M4284 doesn't significantly disrupt the microbiome



# An interesting example that colonization determinants can be targeted to engineer microbiome

