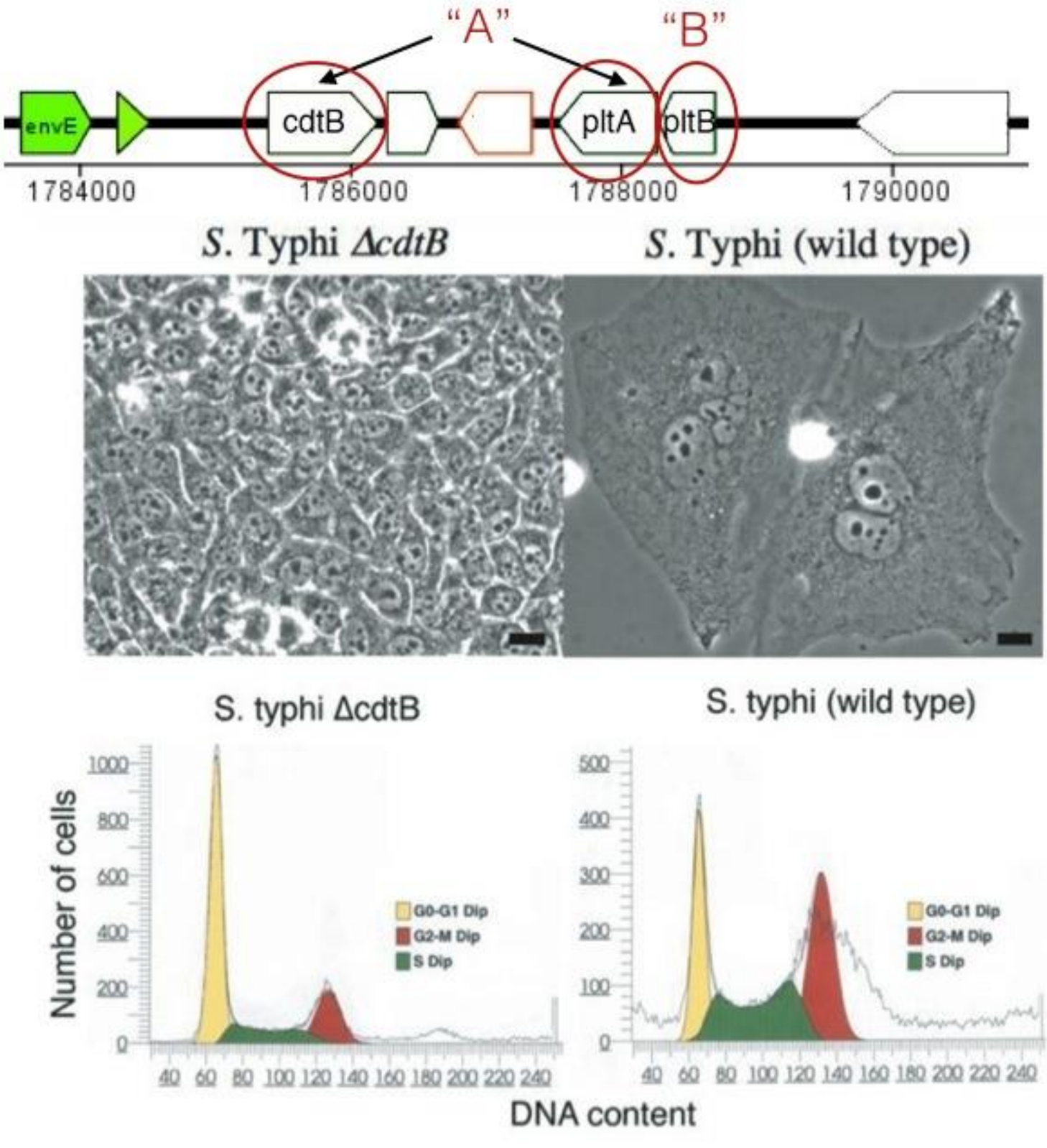
Salmonella typhi and typhoid fever: new insights into an old disease

Two fundamental questions about *Salmonella* Typhi:

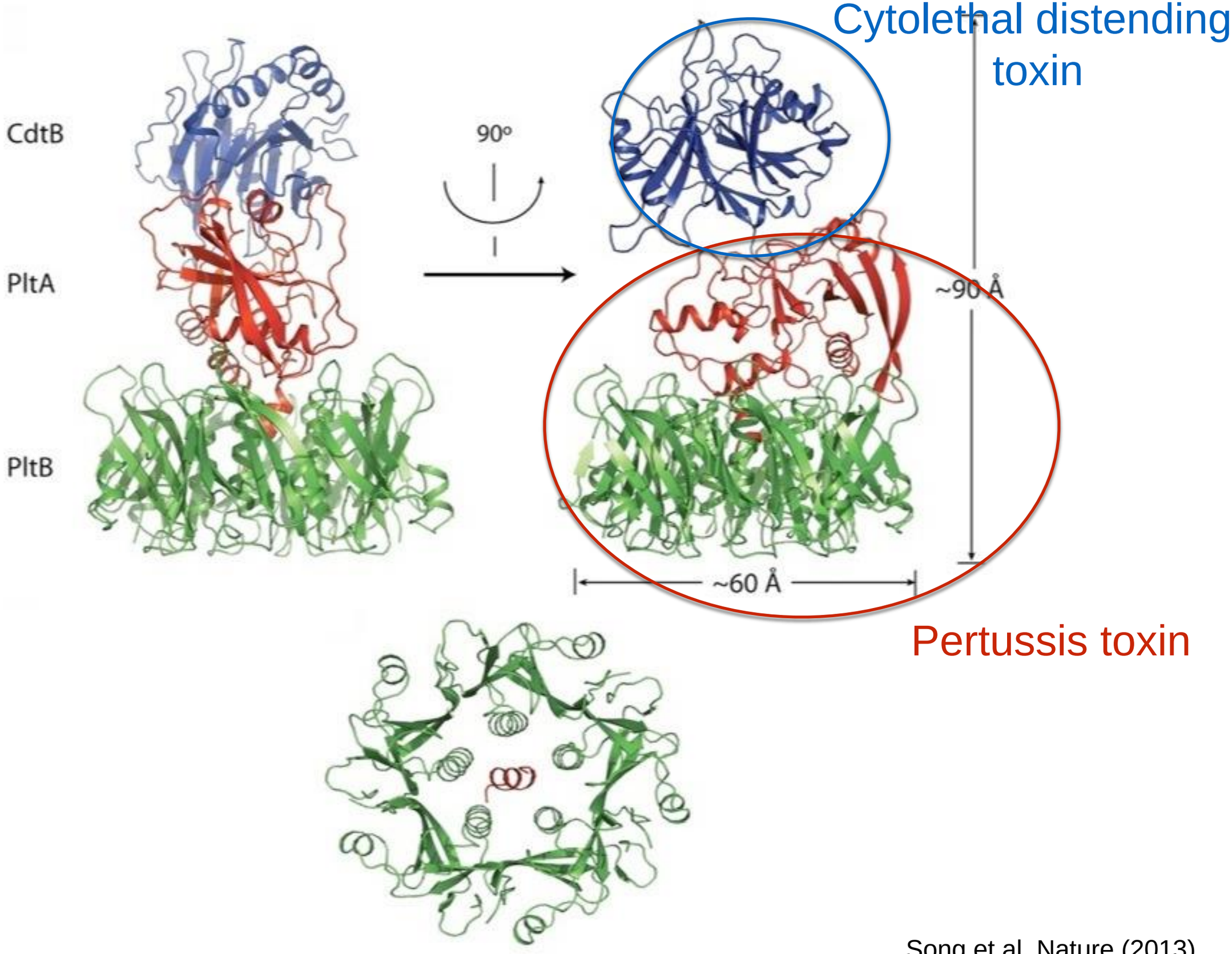
- Why it causes typhoid fever?
- Why it only causes disease in humans?

Typhoid toxin: a unique *Salmonella* Typhi toxin with two active subunits that causes cell cycle arrest in target cells



Haghjo & Galan, PNASc (2004); Spano et al, Cell Host &Microbe (2009); Song et al., Nature (2013)

Typhoid toxin: when two toxins became one

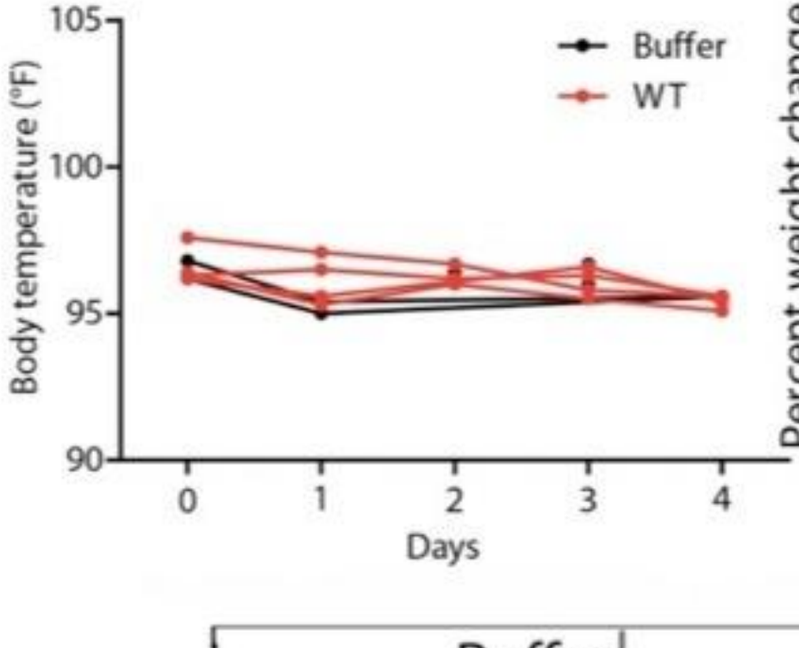


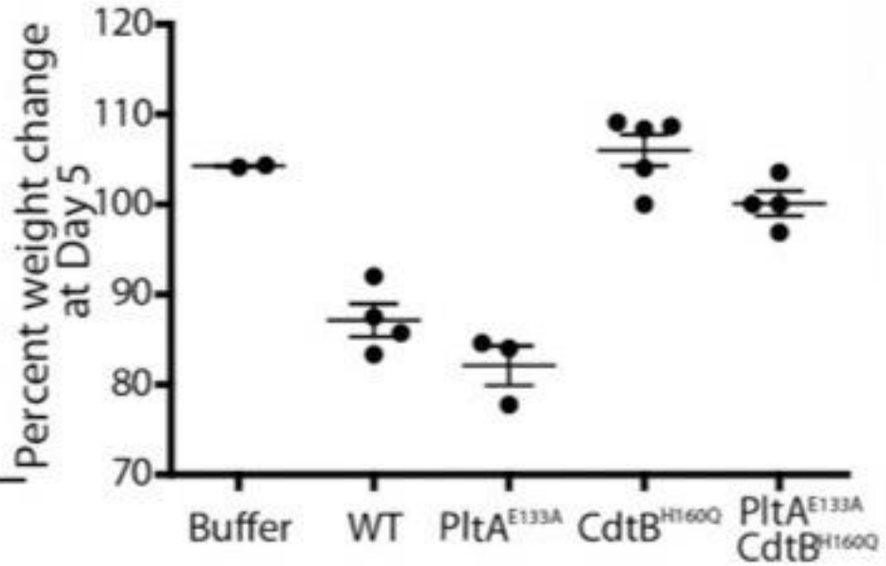
Cytolethal distending toxin

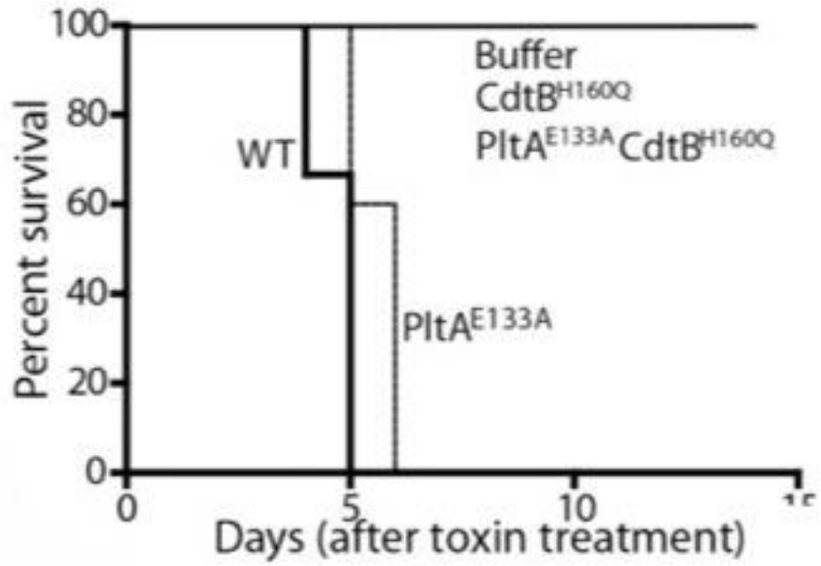
Pertussis toxin

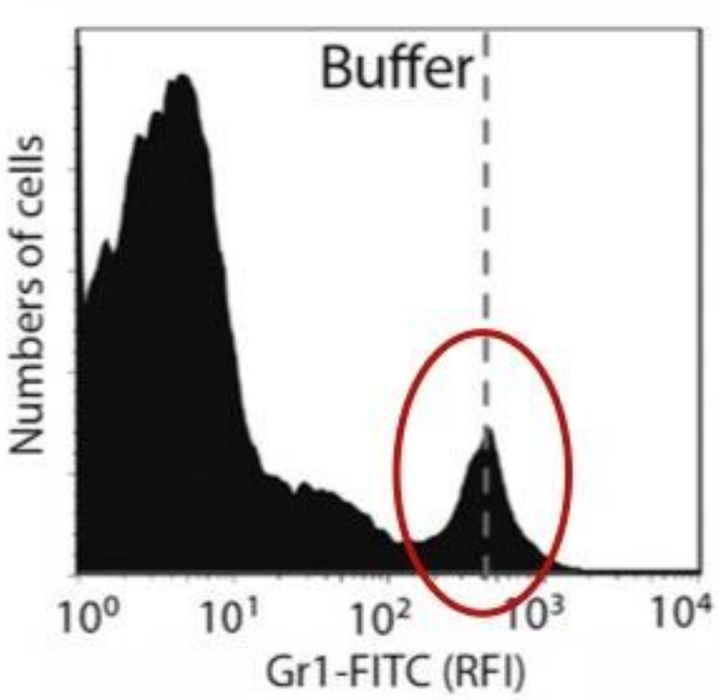
Song et al, Nature (2013)

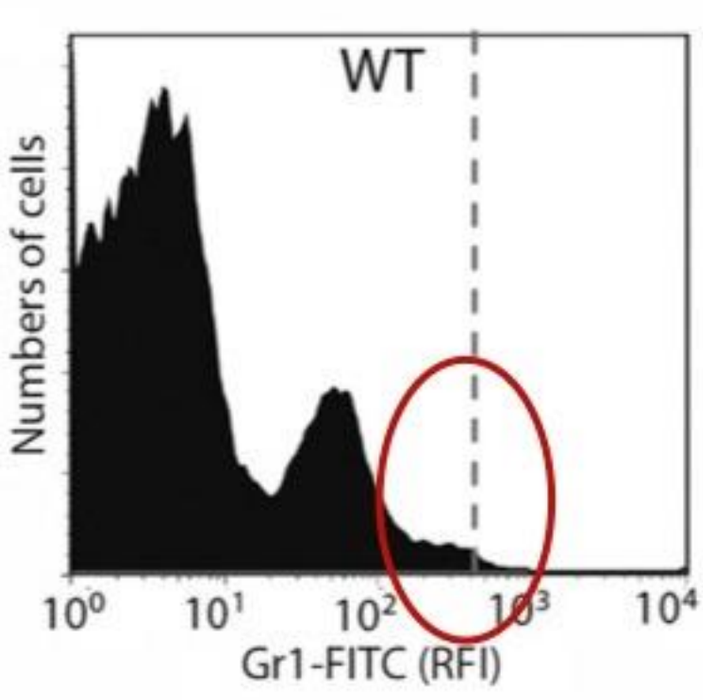
Systemic administration of Typhoid toxin can reproduce many of the symptoms of typhoid fever in an animal model

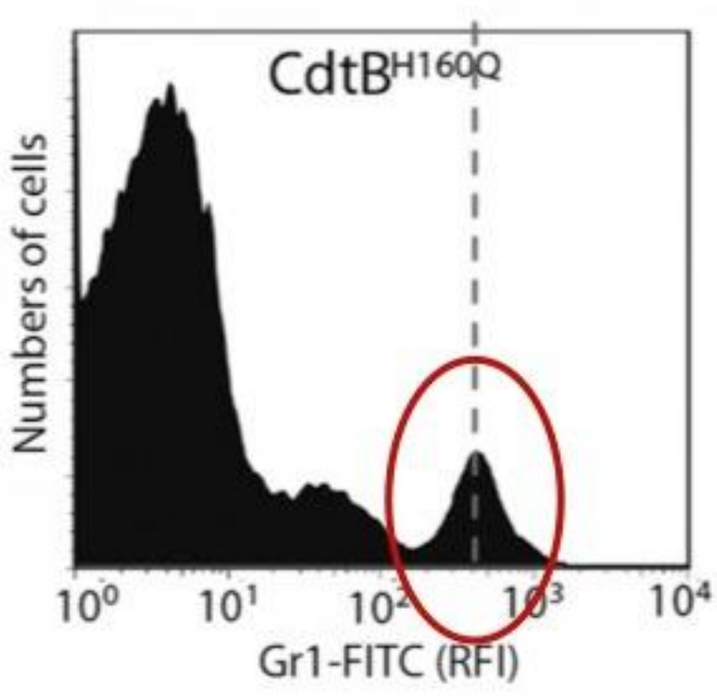












Song et al, Nature (2013)

Two fundamental questions about *Salmonella* Typhi:

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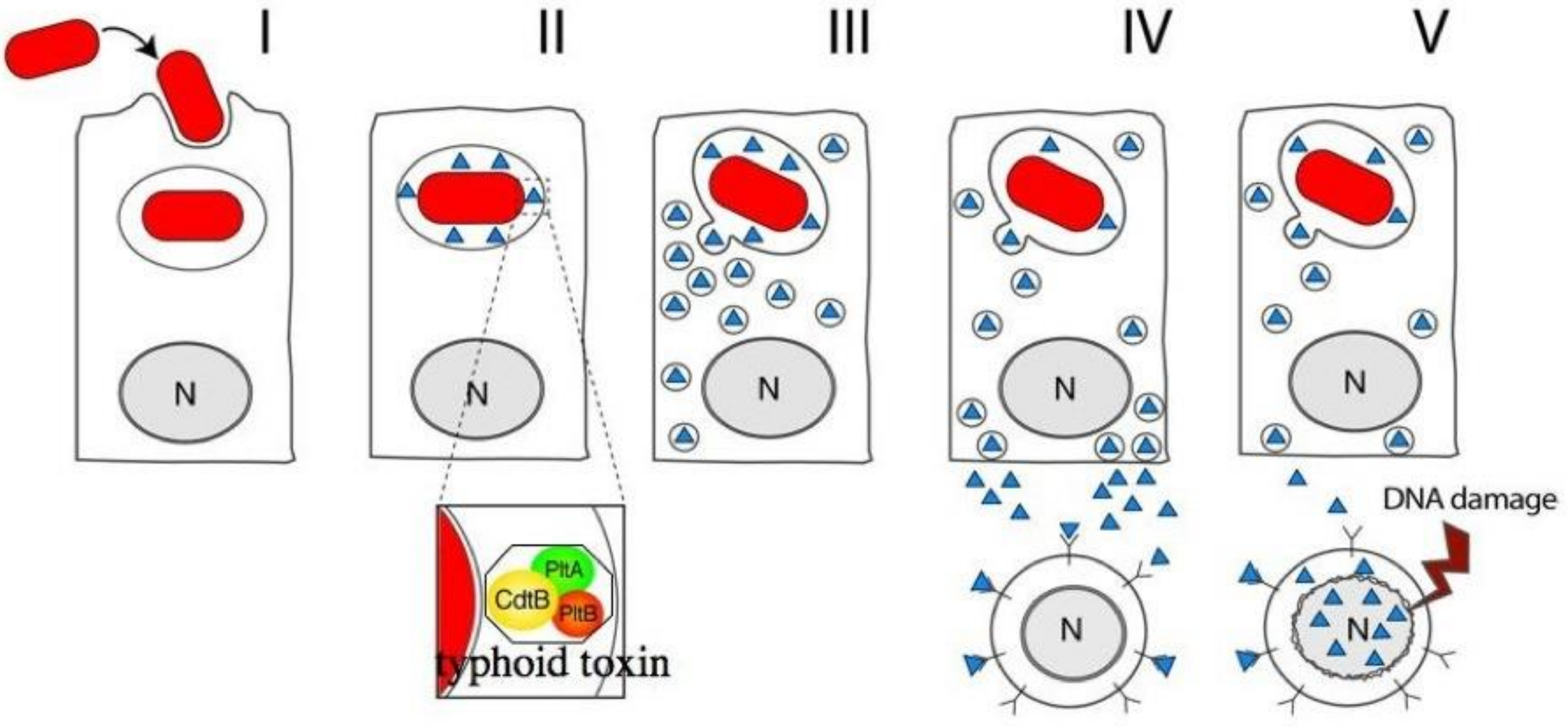
because S. Typhi (and S. Paratyphi) encodes “typhoid toxin”, which is responsible for the pathognomonic symptoms of typhoid fever and is absent from non-typhoidal Samonellae

- Why it only causes disease in humans?

Typhoid toxin: a novel toxin and a novel pathway for exotoxin delivery by an intracellular pathogen



Spano, S., Ugalde, J., and J. E. Galan. Cell, Host &Microbe (2009)

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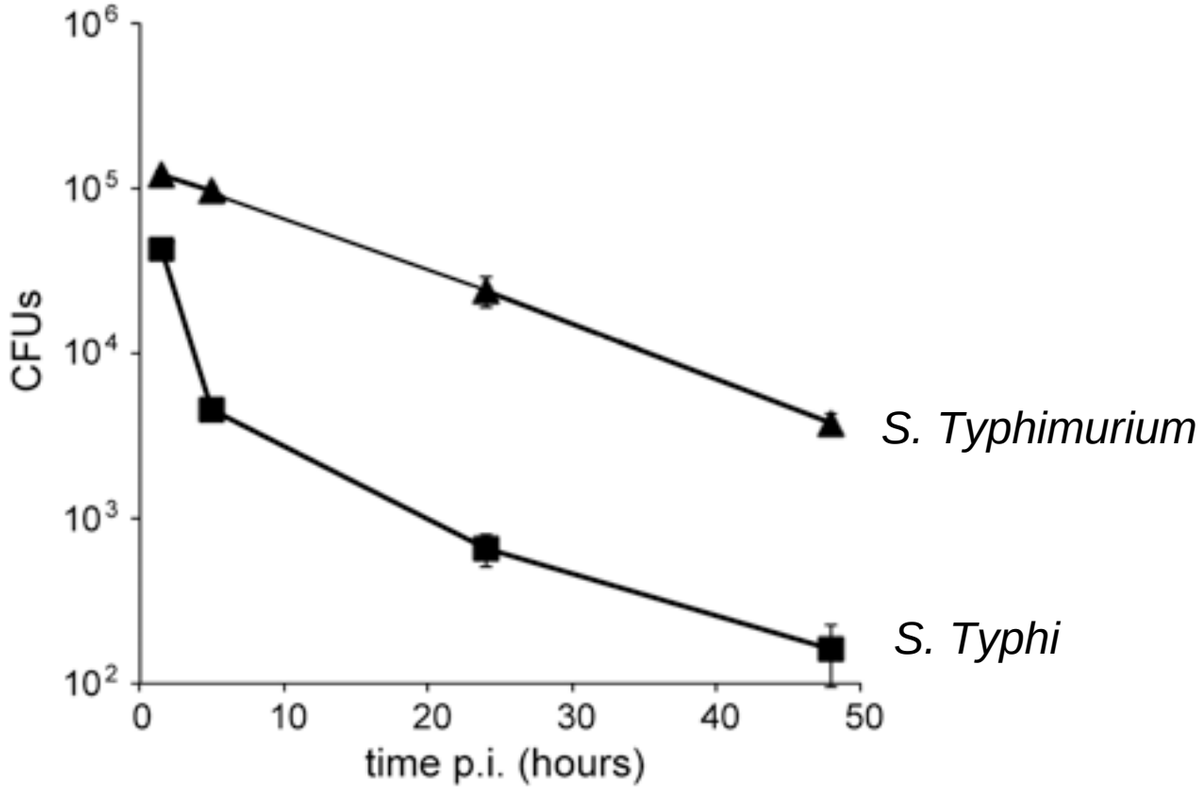
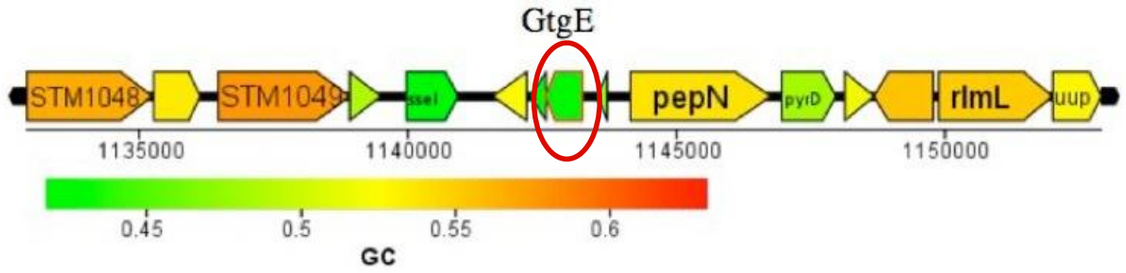
Host restriction is manifested at the cellular level: *Salmonella typhi* does not survive within mouse macrophages

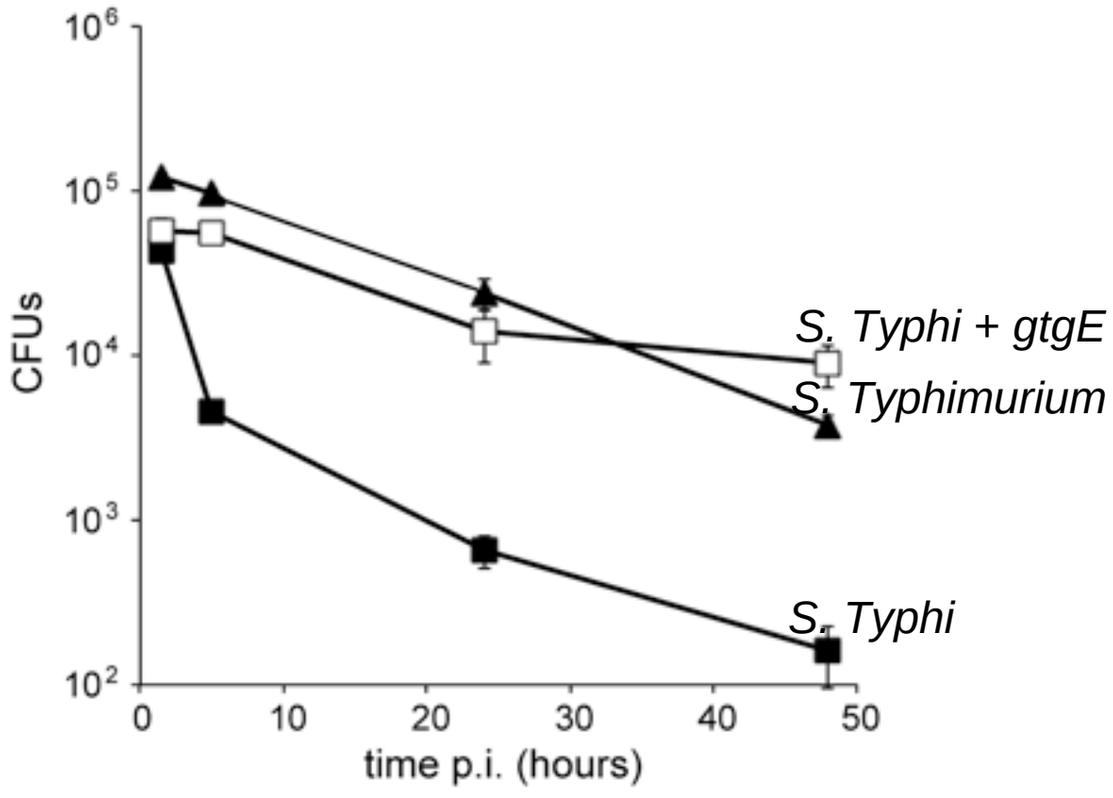


Spano & Galan, PNASc (2012); Science (2013)

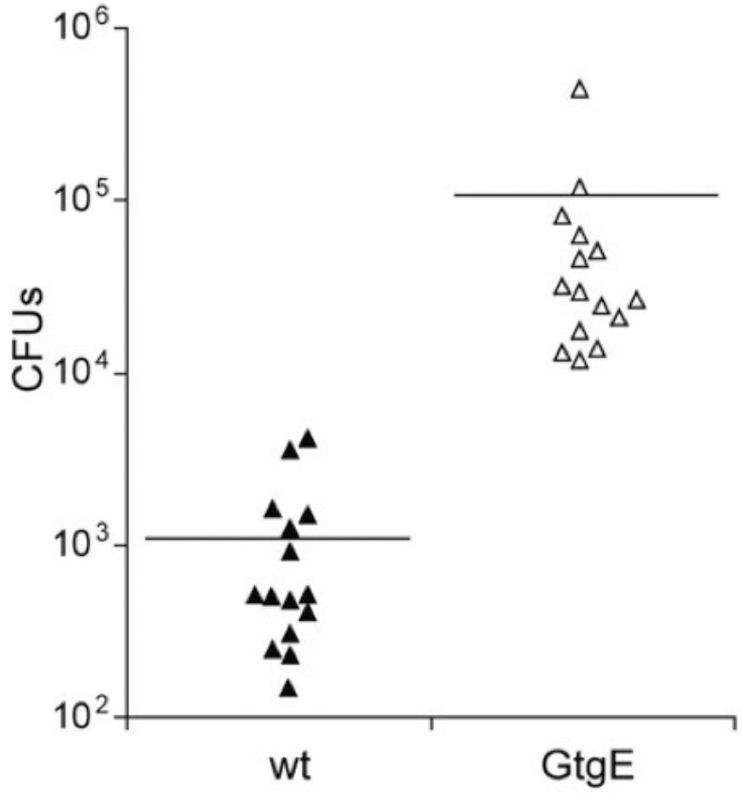
Expression of single *Salmonella Typhimurium* gene, *gtgE*, allows *Salmonella Typhi* to overcome host restriction in mouse macrophages (*in vitro*) and mouse tissues (*in vivo*)



mouse macrophages

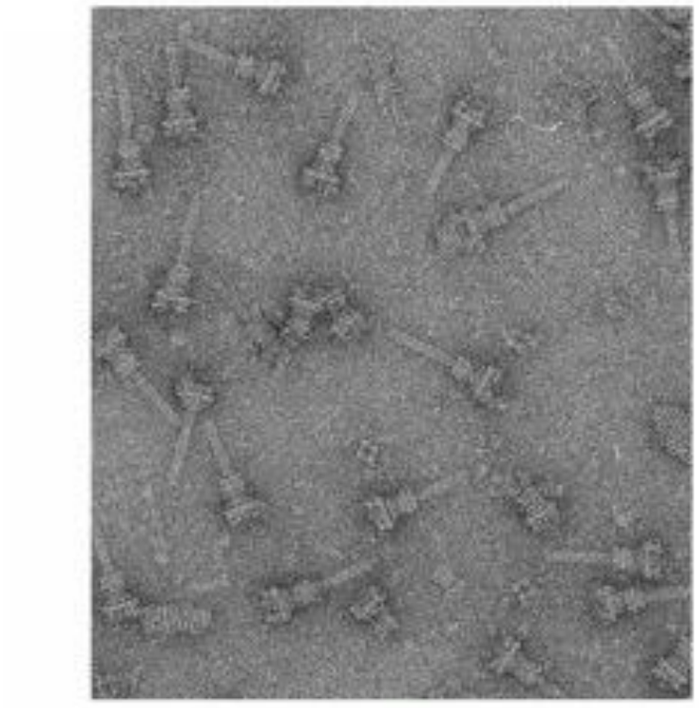


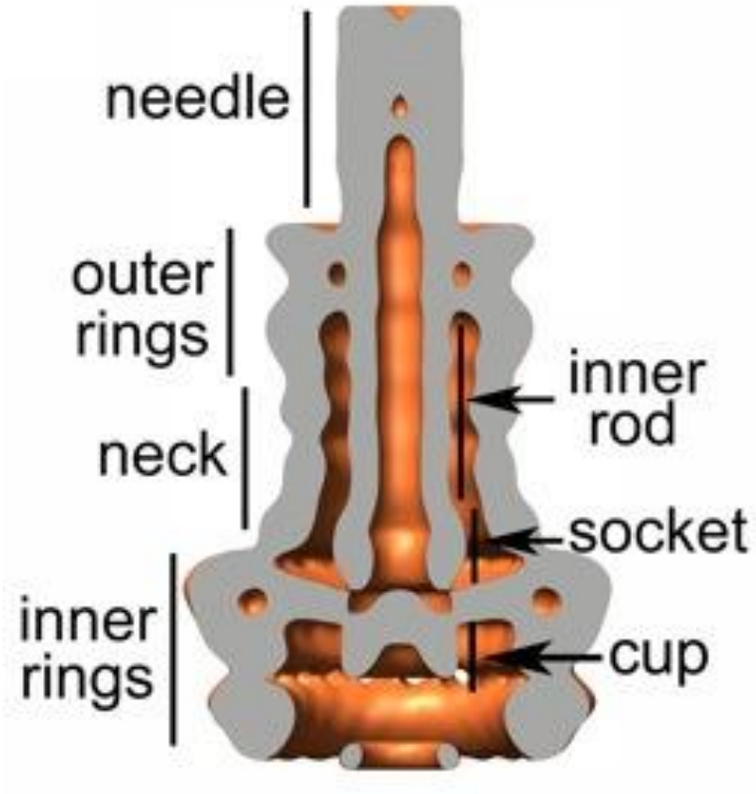
mouse spleens

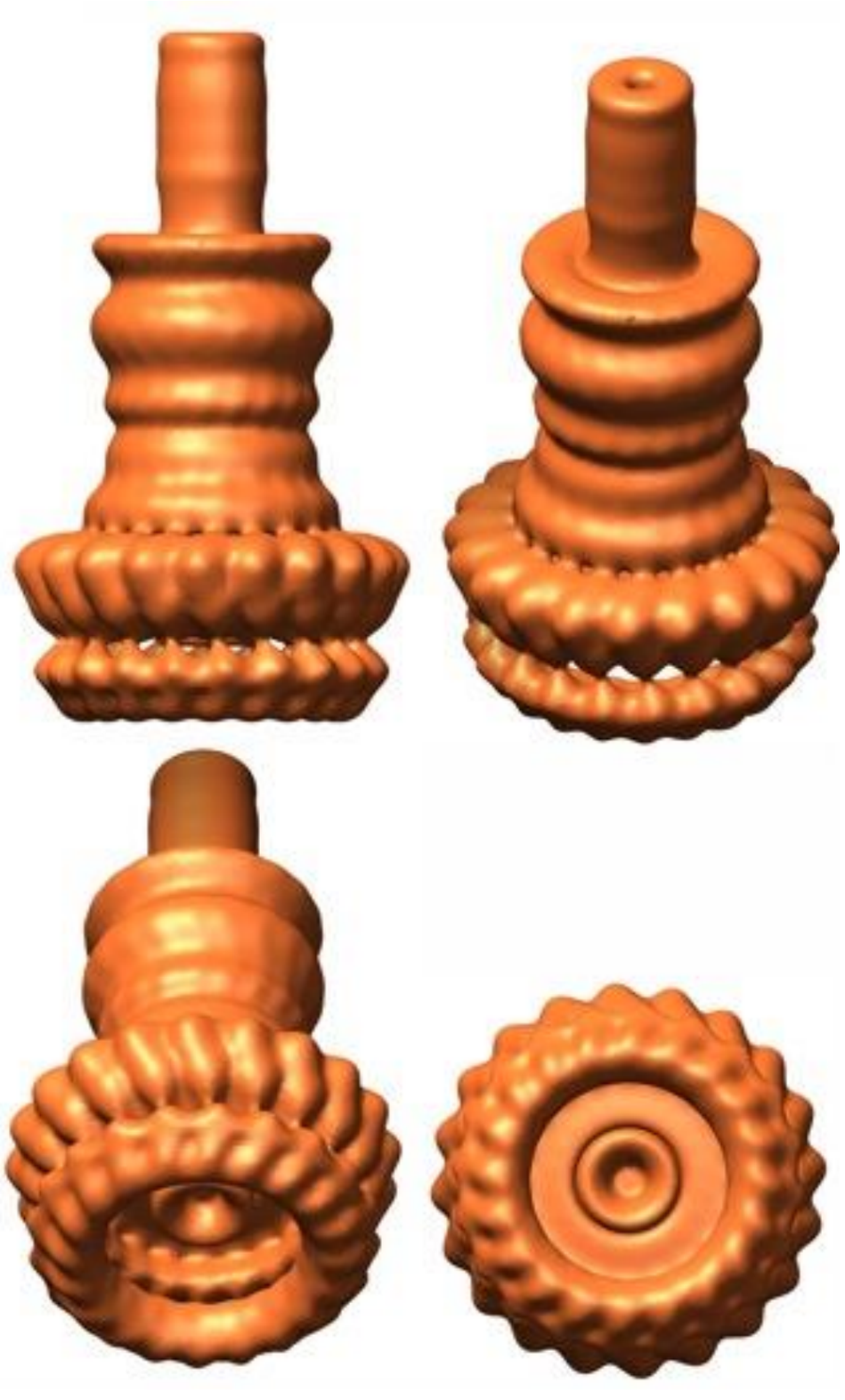


Spano & Galan, PNASc (2012); Science (2013)

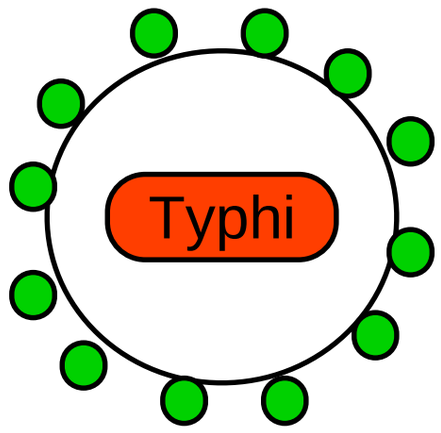
Salmonella type III secretion system: a molecular machine for protein delivery into host cells



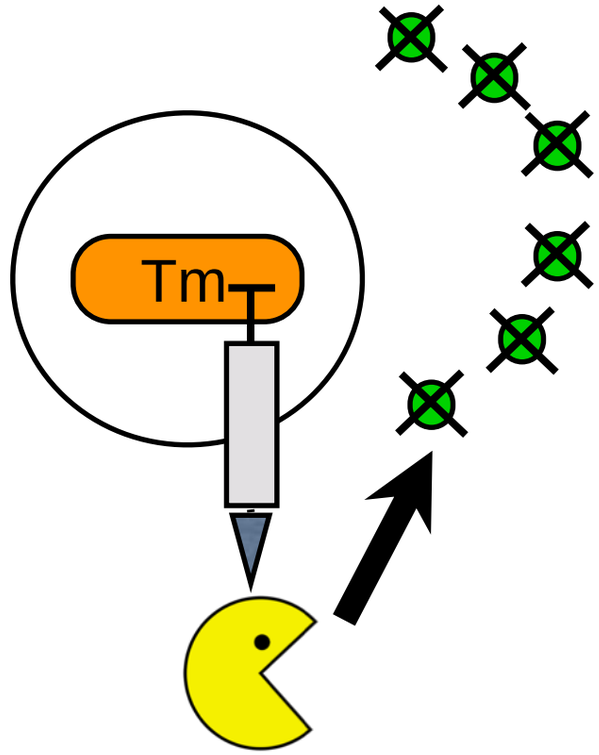




GtgE extends host range by proteolytically removing Rab29, Rab32, and Rab38 from the Salmonella-containing vacuole

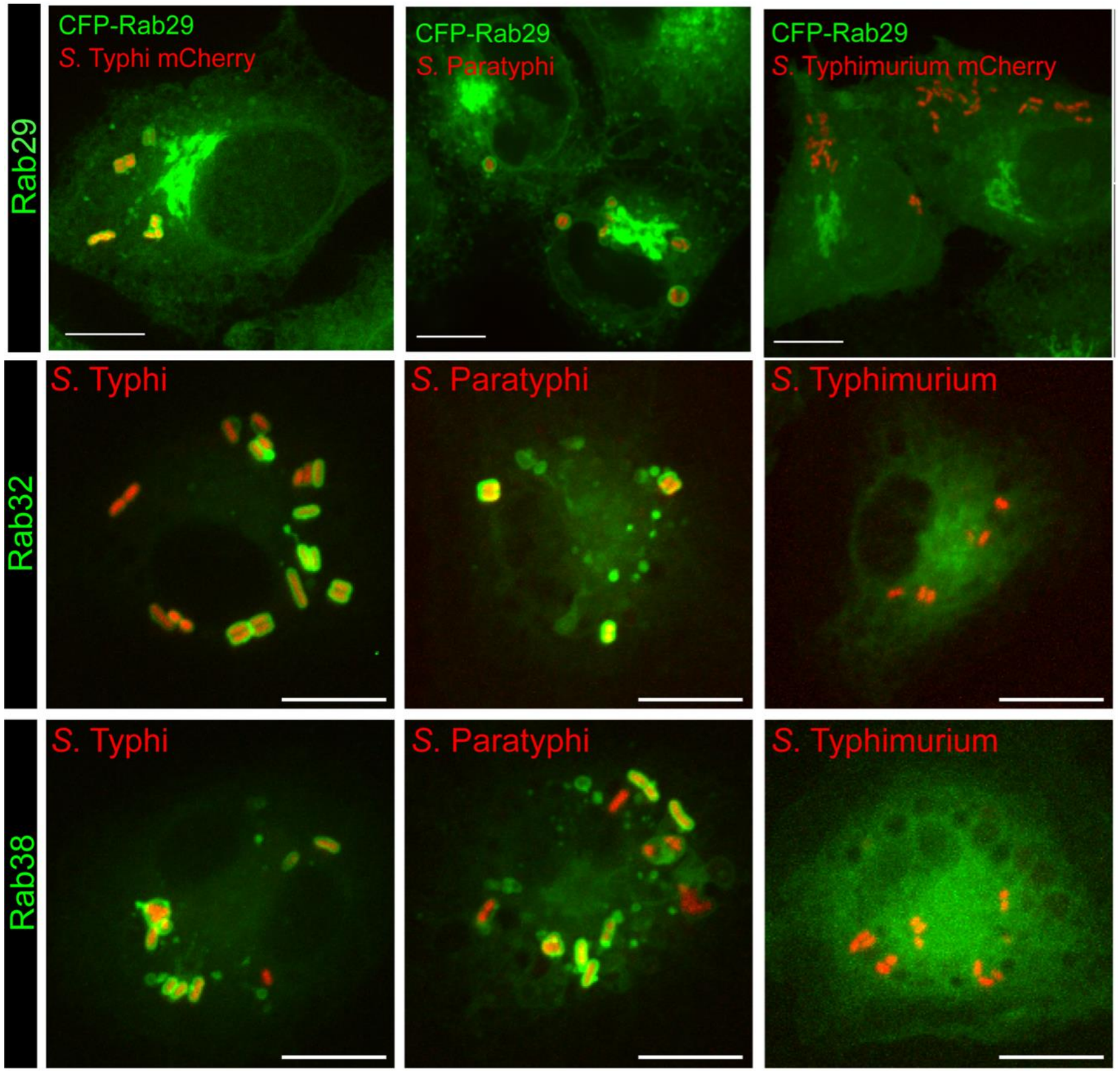


=Rab29/32/38

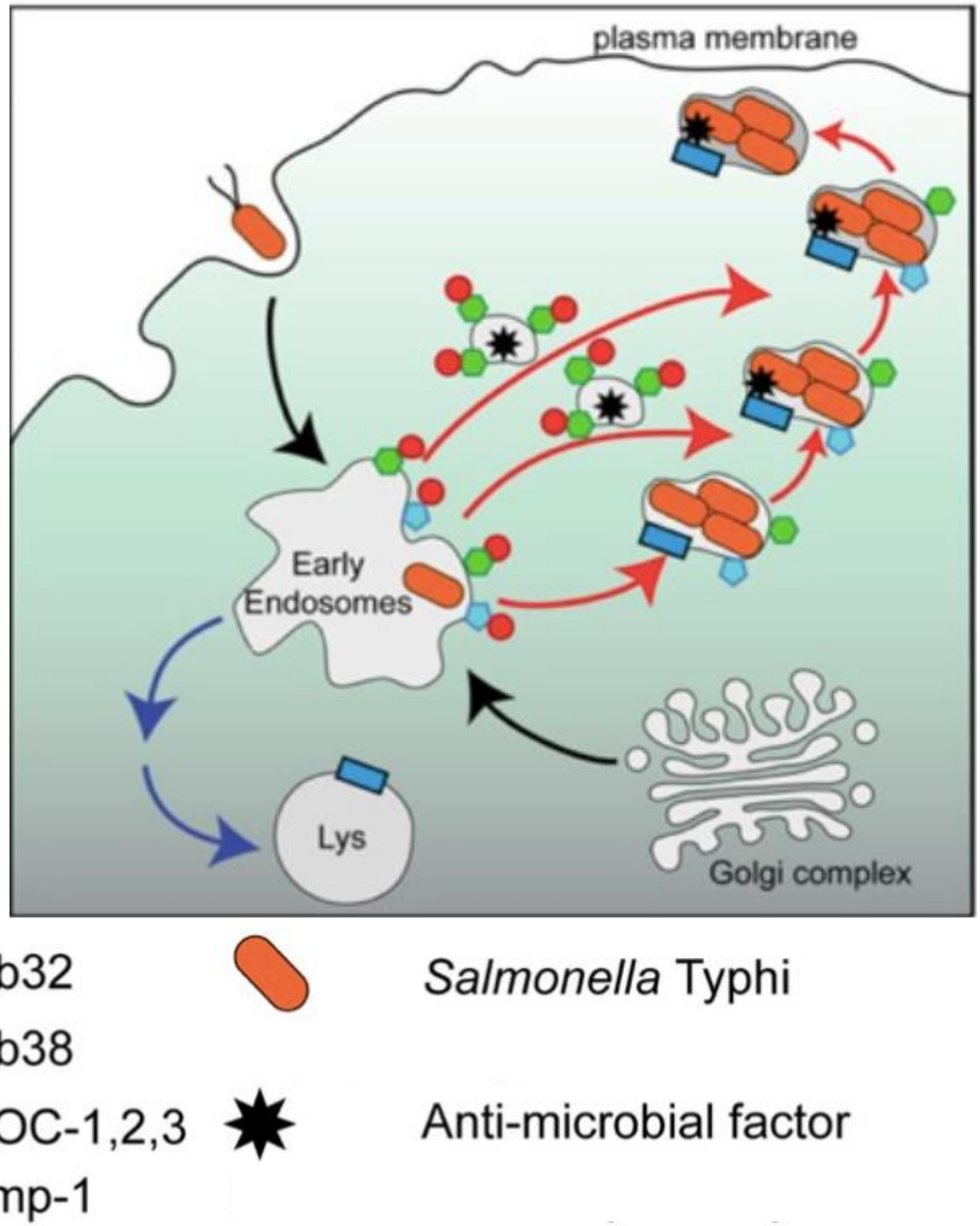


GtgE

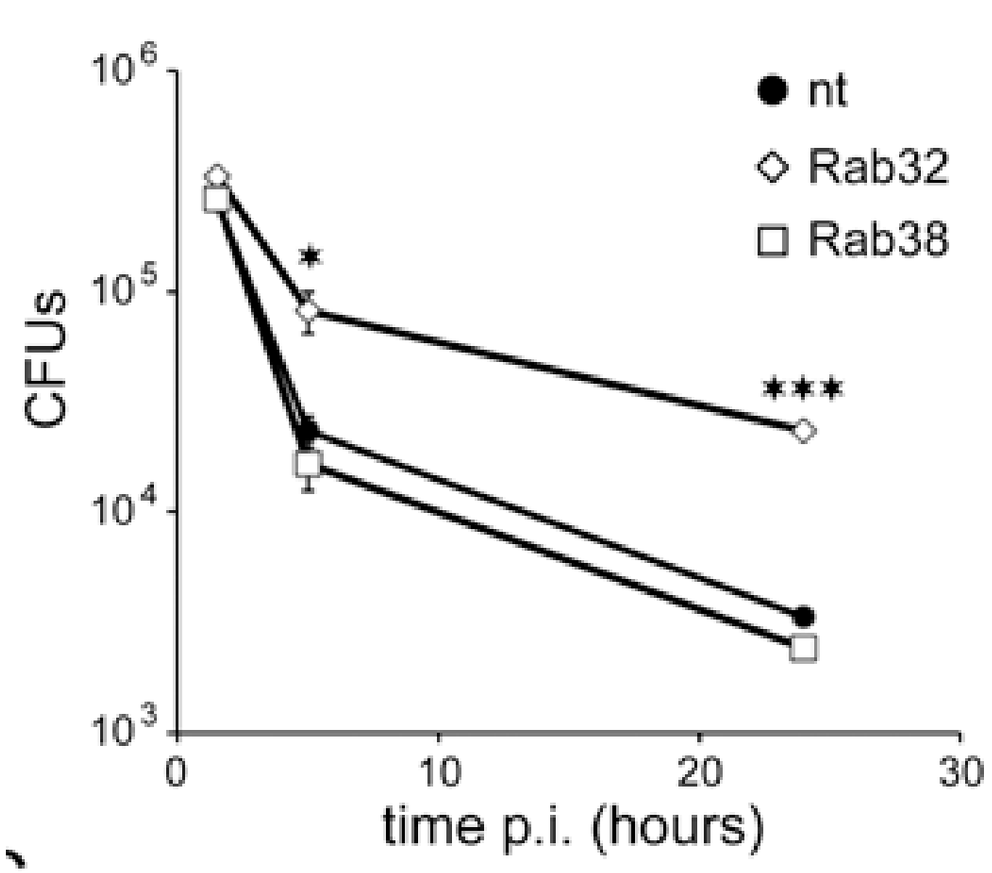
Rab29, Rab32, and Rab38 localize to the human-adapted *S. typhi* and *S. paratyphi*-containing vacuoles but not to vacuoles harboring *S. typhimurium*



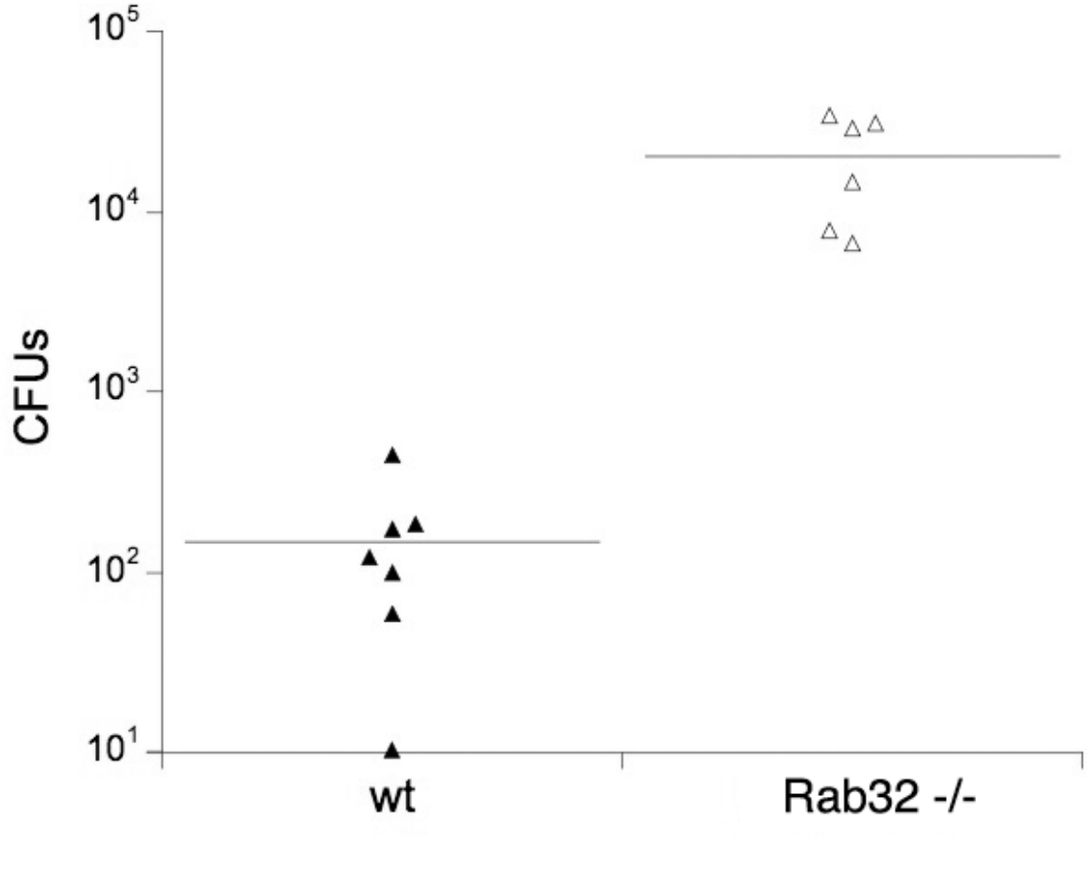
Rab32/Rab38 delivers antimicrobial factors to the *Salmonella*-containing vacuole in macrophages



Removal of Rab32 allows *Salmonella typhi* survival in mouse macrophages and tissues



RNAi-mediated depletion in macrophages



S. typhi in spleens of infected mice

Spano & Galan, Science (2013)

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because S. Typhi (and S. Paratyphi) encodes "typhoid toxin", which is responsible for the pathology and symptoms of typhoid fever

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STUDIES ON INFECTION AND IMMUNITY IN EXPERIMENTAL TYPHOID FEVER

I. Typhoid Fever in Chimpanzees Orally Infected with Salmonella typhosa

By GEOFFREY EDSALL, M.D., SIDNEY GAINES,* Ph.D., MAURICE LANDY,‡ Ph.D., W. D. TIGERTT,§ M.D., HELMUTH SPRINZ,§ M.D. R.-J. TRAPANI,‡ Ph.D., ADRIAN D. MANDEL,‖ Ph.D., and A. S. BENENSON,¶ M.D.

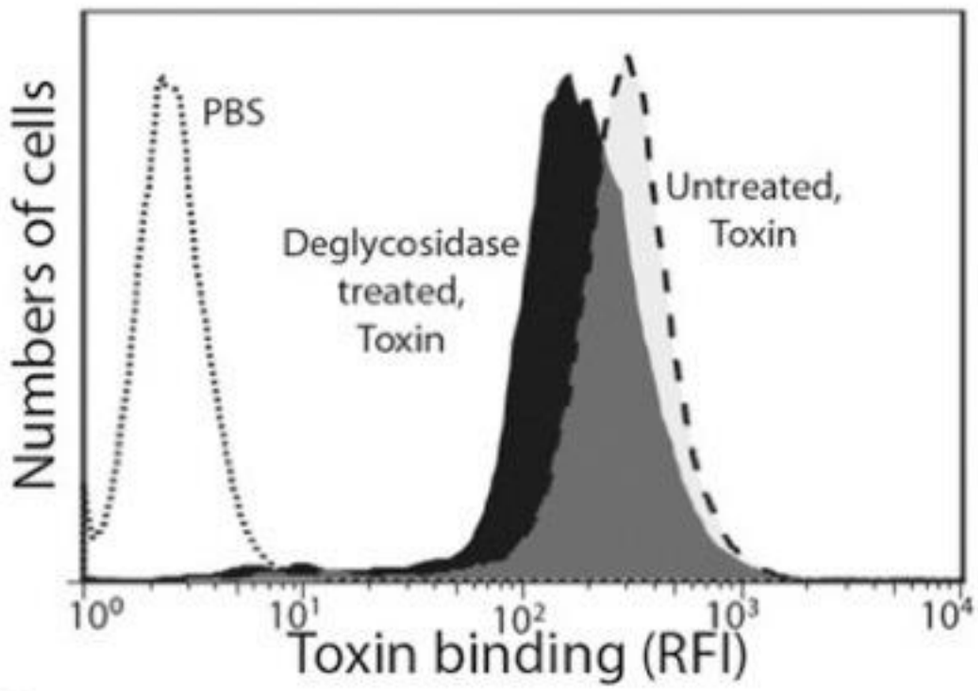
(*From the Walter Reed Army Institute of Research, Washington, D. C.*)

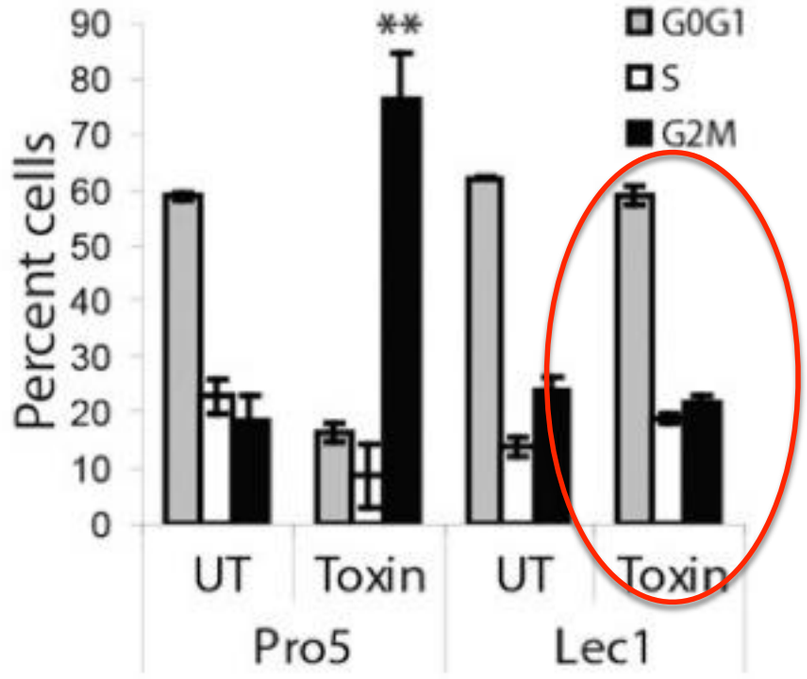
Plates 6 and 7

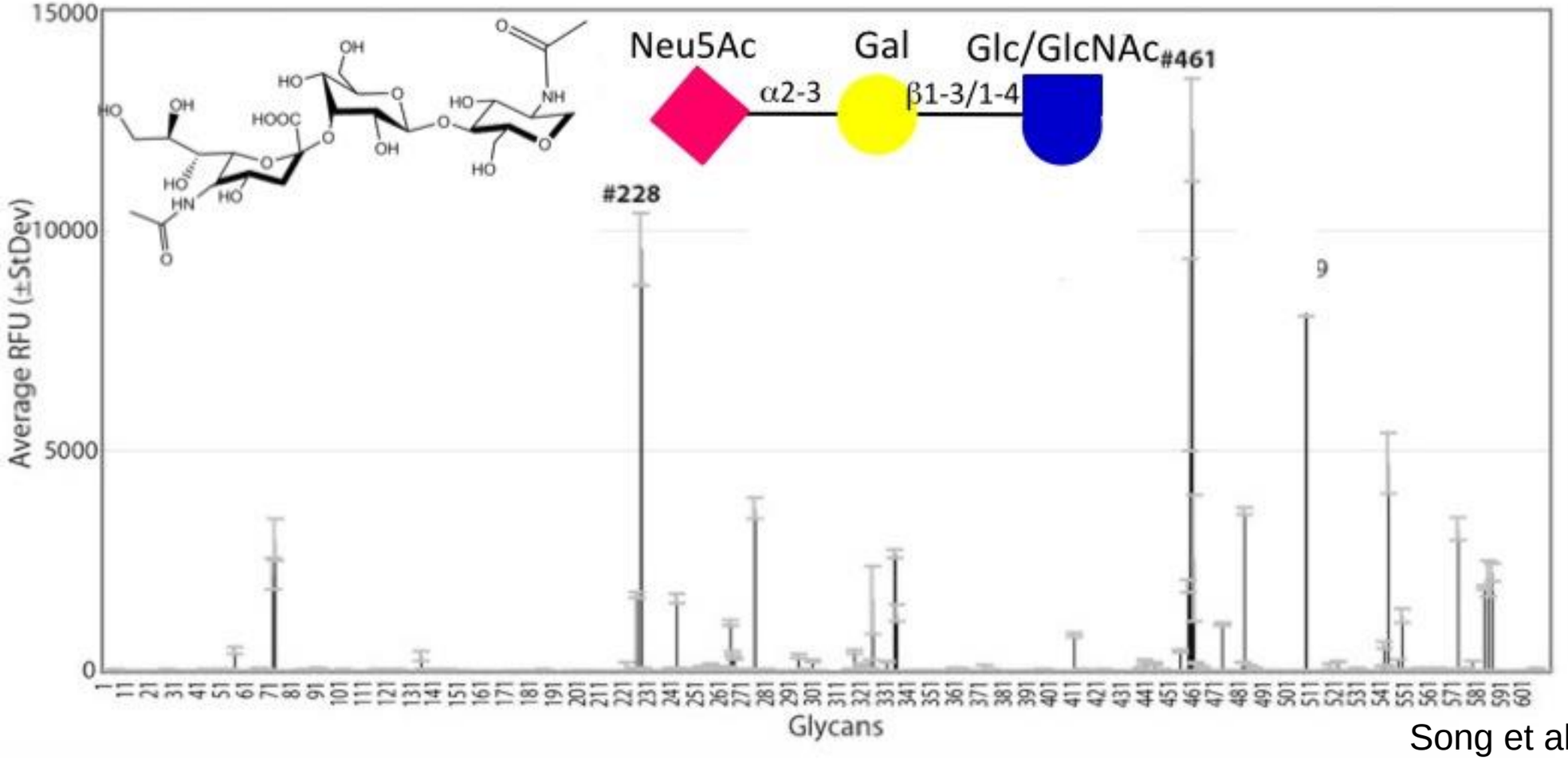
(Received for publication, February 29, 1960)

The principal apparent differences between typhoid fever as seen in our chimpanzees and in man were the incubation period, which was relatively short in the chimpanzees, and the clinical course of the disease, which in the chimpanzees was relatively mild and brief. Only a few animals in the whole series appeared seriously ill during the course of the infectious process. The hypertoxicity, typhoid facies, stupor, extreme lethargy, etc., which are so generally associated with the disease in man were not discernible in our infected chimpanzees. Finally, the pathological changes, although wholly typical of mild

Typhoid toxin recognizes terminally sialylated glycans on specific surface glycoproteins (Podocalixin 1 and CD45) on target cells



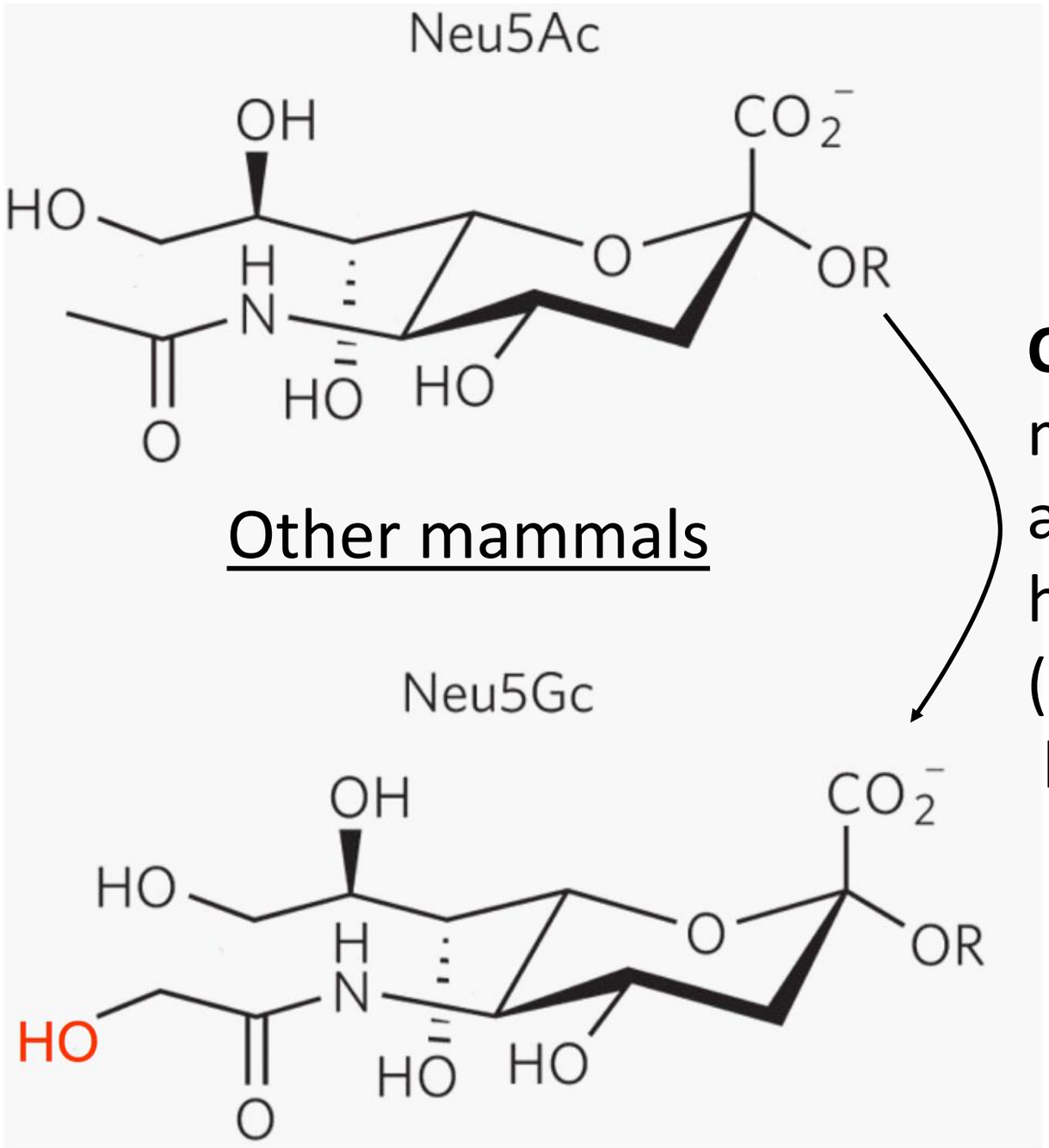




Song et al, Nature (2013)

Two major sialic acids in mammalian cells:

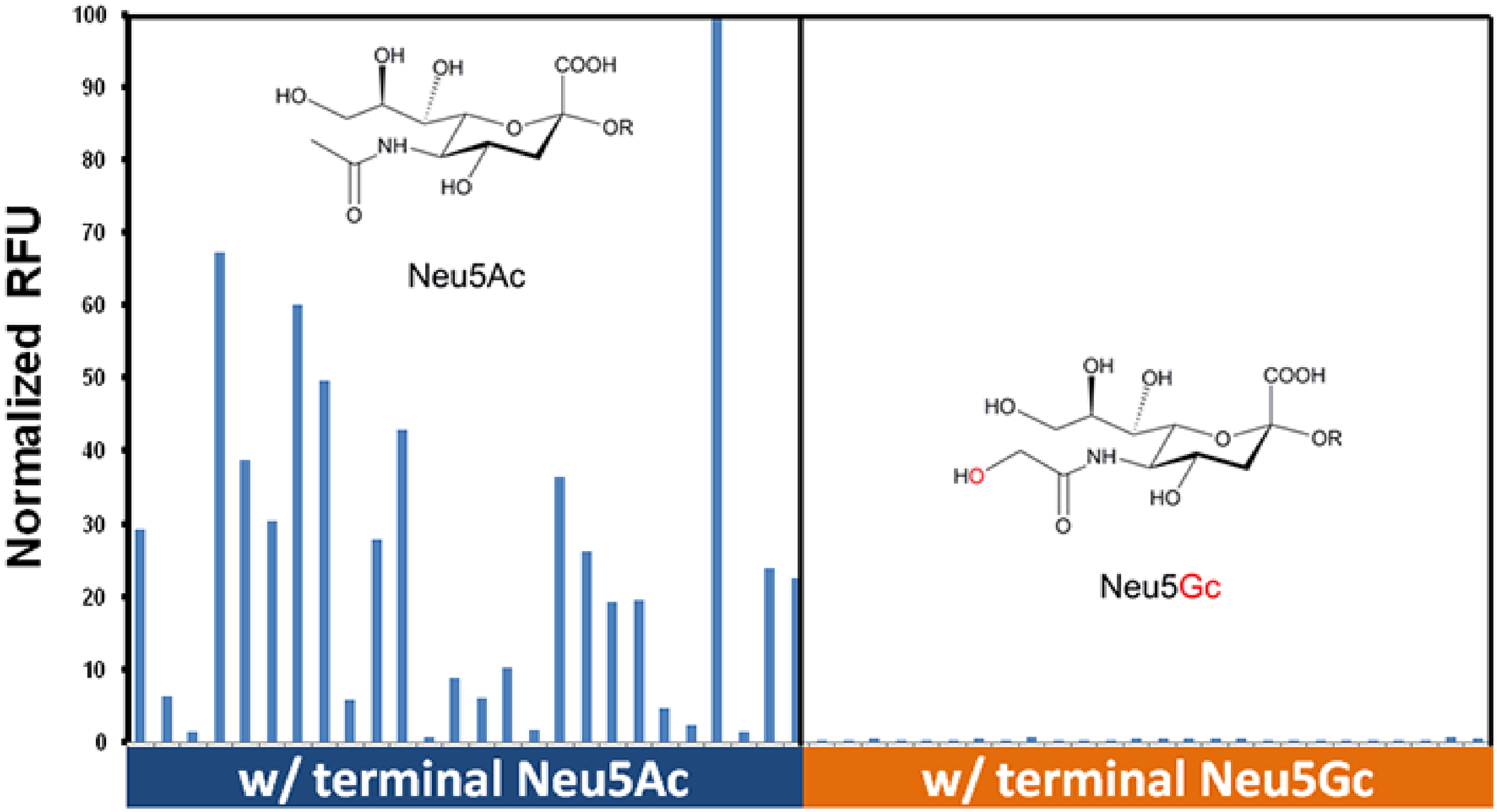
Humans



CMAH (cytidine monophospho-N-acetylneuraminic acid hydroxylase) (pseudogene in humans)

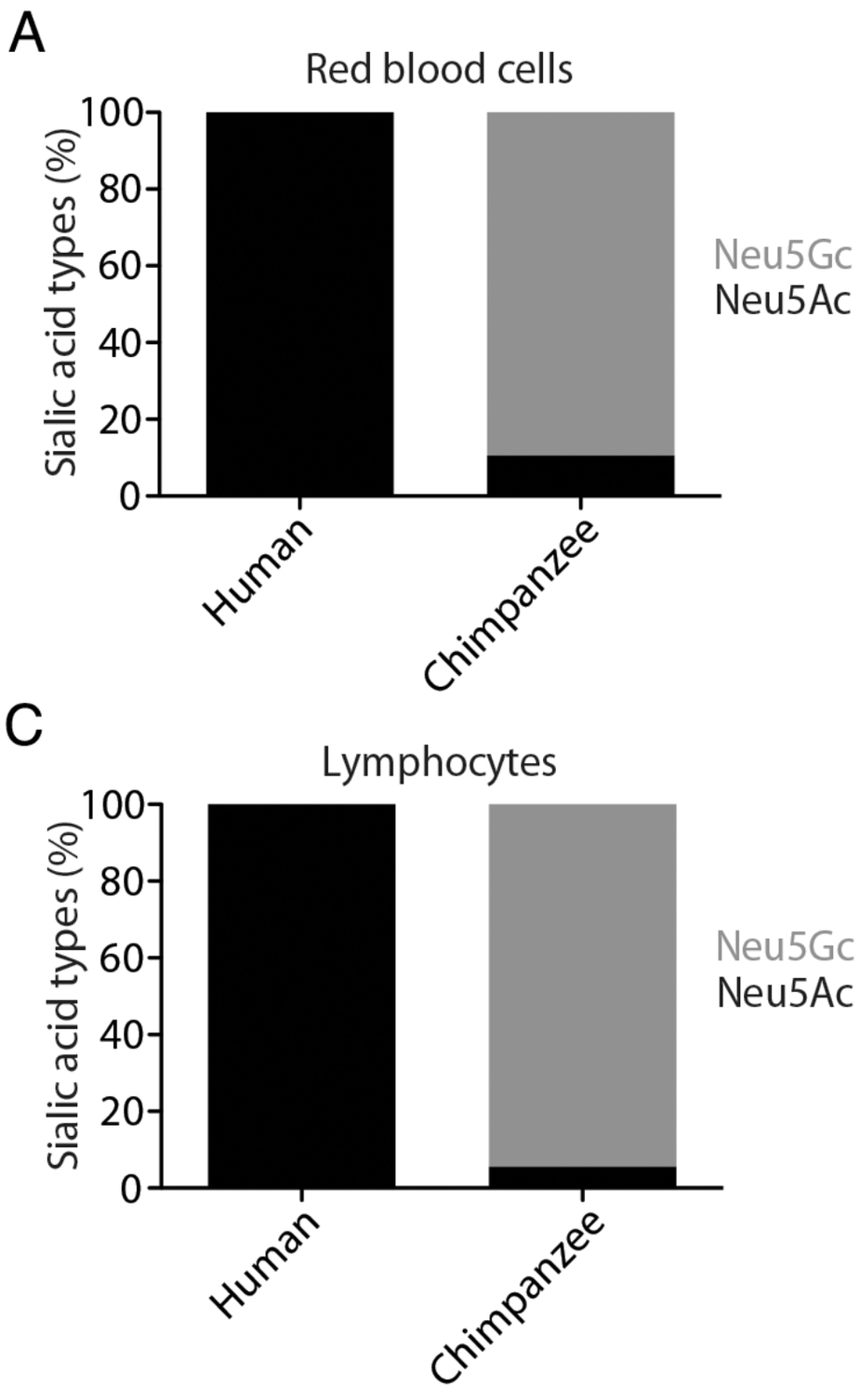
Other mammals

Typhoid toxin binds Neu5Ac- but not Neu5Gc-terminated glycans



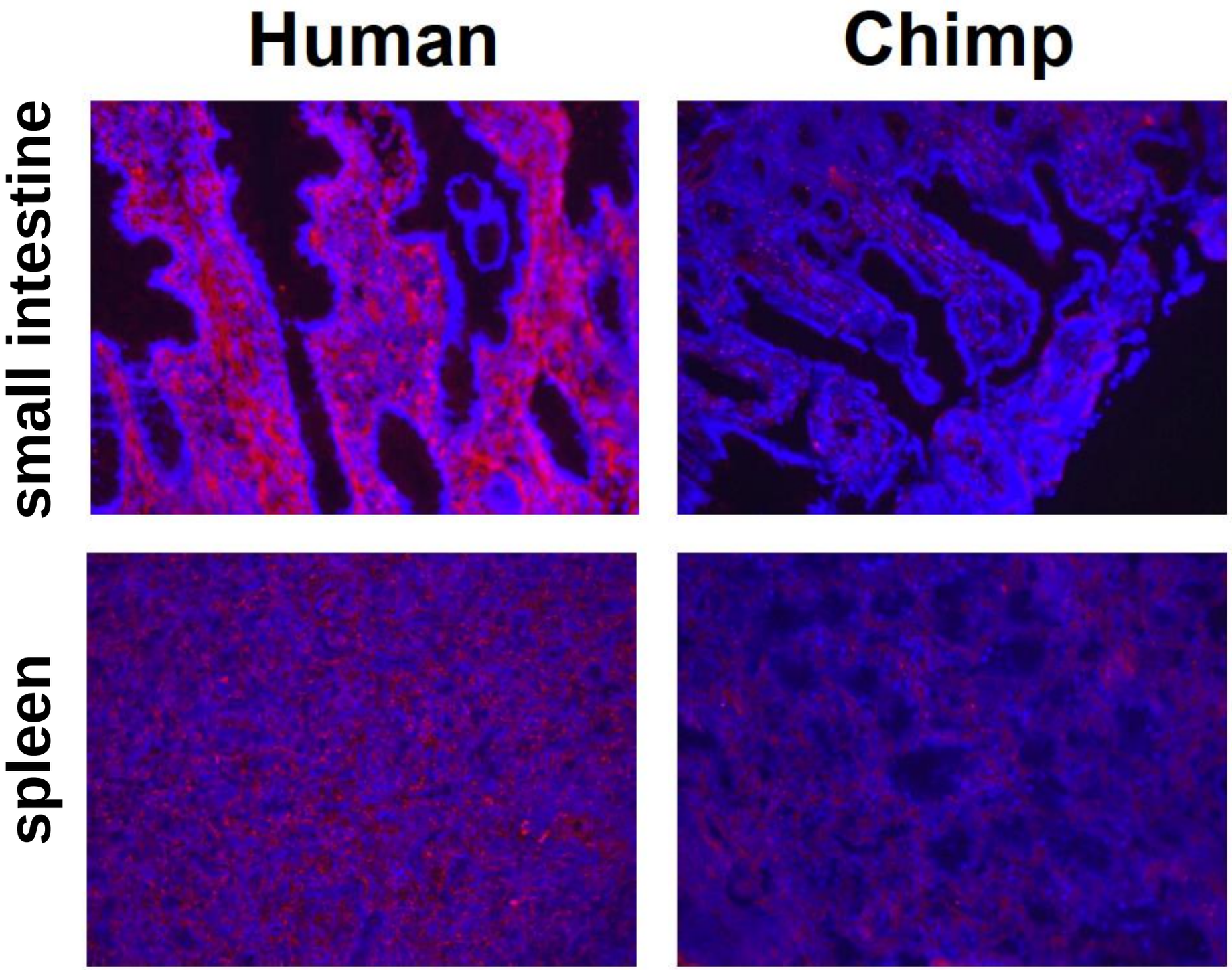
Deng et al, Cell (in press)

Typhoid toxin does not bind to chimpanzee cells



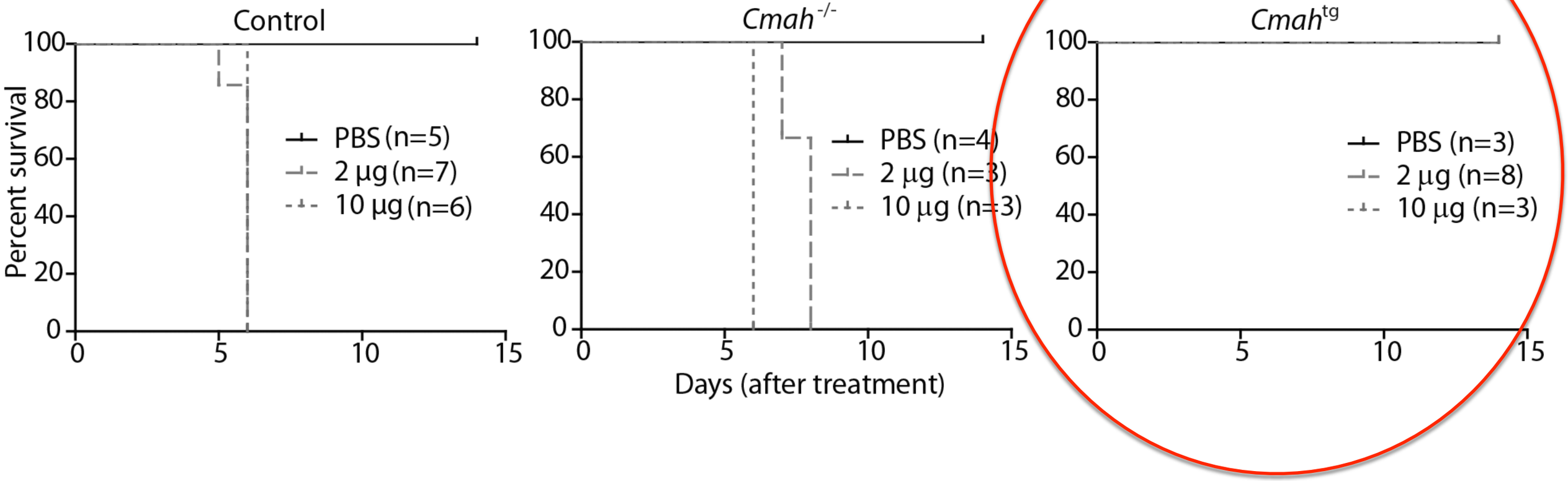
Deng et al, Cell (in press)

Typhoid toxin binds to human but not to chimpanzee tissues



Deng et al, Cell (in press)

Constitutive expression of *cmah* renders mice completely resistant to typhoid toxin



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Furthermore, disease can only occur in humans because they are the only species that uniquely express Neu5Ac-terminated glycans, which are the receptors for typhoid toxin, while other mammals predominantly express Neu5Gc-terminated glycans, which are not permissive for typhoid toxin binding


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