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Prophage taming by the adherent-invasive *Escherichia coli* LF82 upon macrophage infection

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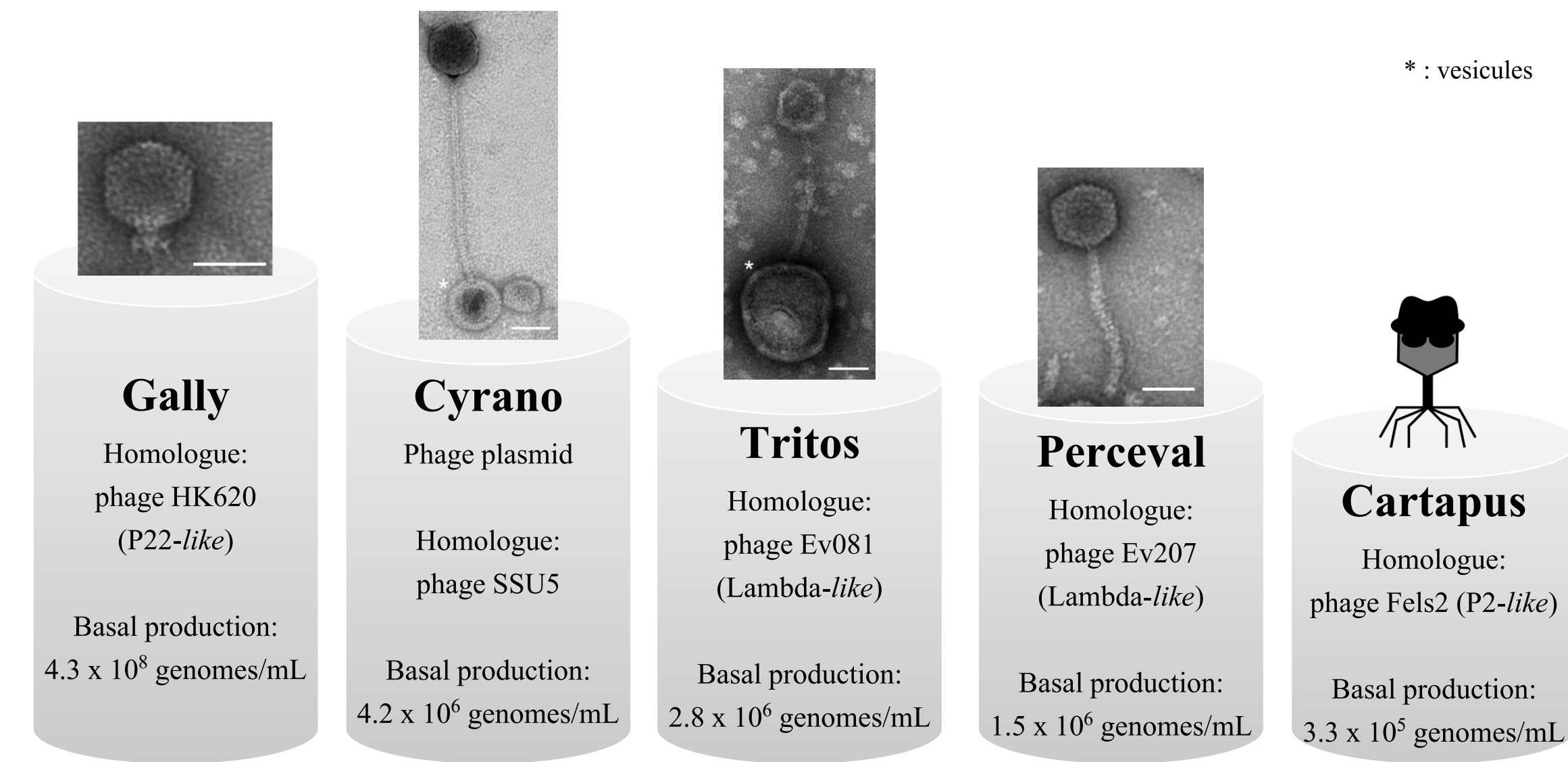
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Escherichia coli LF82 is an adherent-invasive pathogen (AIEC) frequently found in the gut microbiota from Crohn's disease patients. This bacterium is able to survive and multiply inside macrophages, where it sustains the gut inflammation. In order to see if prophages could be involved in the physiology of *E. coli* LF82, we first characterized *in vitro* the five prophages identified in this strain [1, 2]. The most expressed of them, a P22 homologue called Gally, is strongly associated with *E. coli* strains from Crohn's disease patients [3]. Finally, to further understand the good survival of *E. coli* LF82 in macrophages, we extended the study of its prophages after macrophage infection.

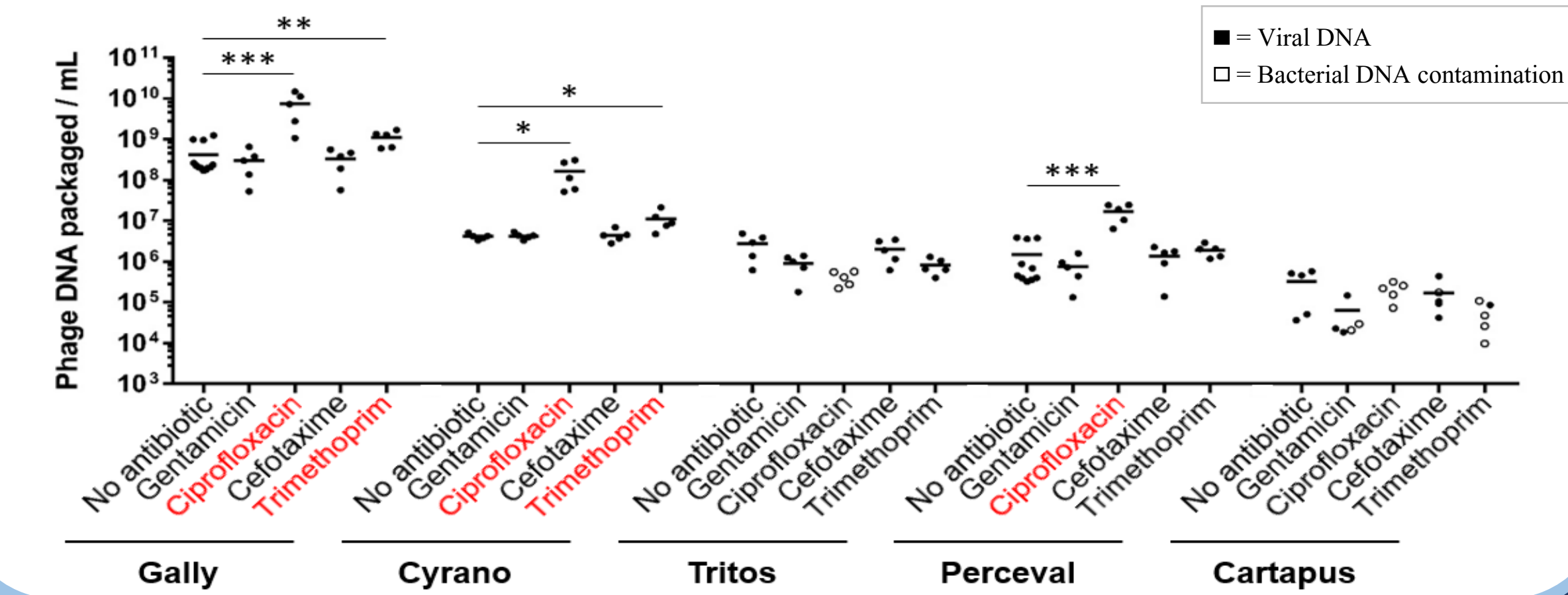
Escherichia coli LF82 virome

The 5 prophages from *E. coli* LF82 are active



Gally and Cyrano prophages are induced after genotoxic stress

Phage quantification (qPCR)



Are these prophages involved in *E. coli* LF82 virulence ?

E. coli LF82 prophages encode various morons

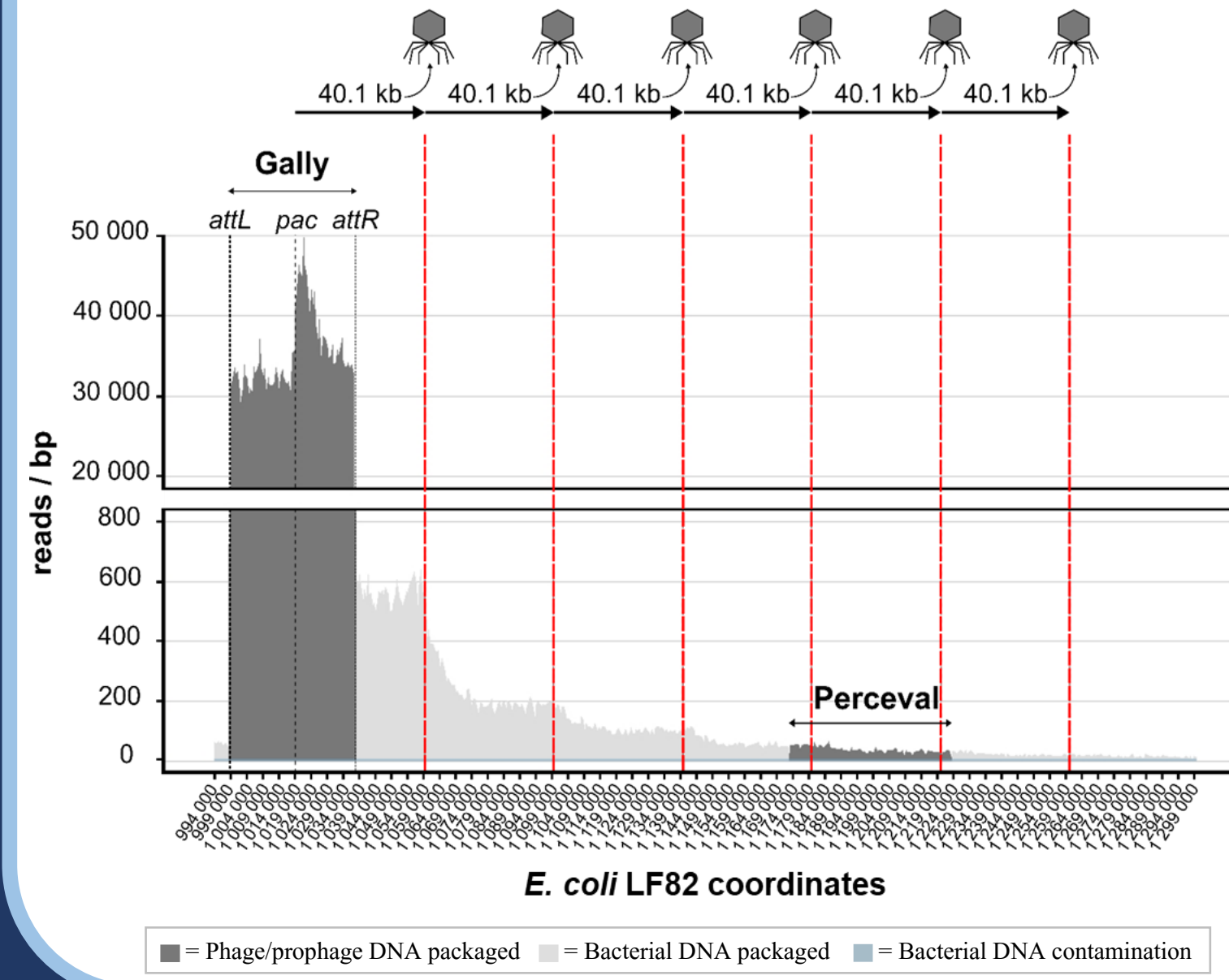
30 morons identified (after *in vitro* cultures of *E. coli* LF82 in LB and DMEM media, transcriptomic analysis)

Morons	Gally	Cyrano	Tritos	Perceval	Cartapus
Hypothetical proteins	-	5	1	2	4
Annotations	-	HicA, HicB, RelE/ParE, Antitoxine putative, KacT	Ydfk, GnsB, Cspl, CspB, HokD, ImmA/IrrE metallo-endopeptidase	SitABCD, EmrE, TonB	Exonuclease
Total number of morons	0	12	7	6	5

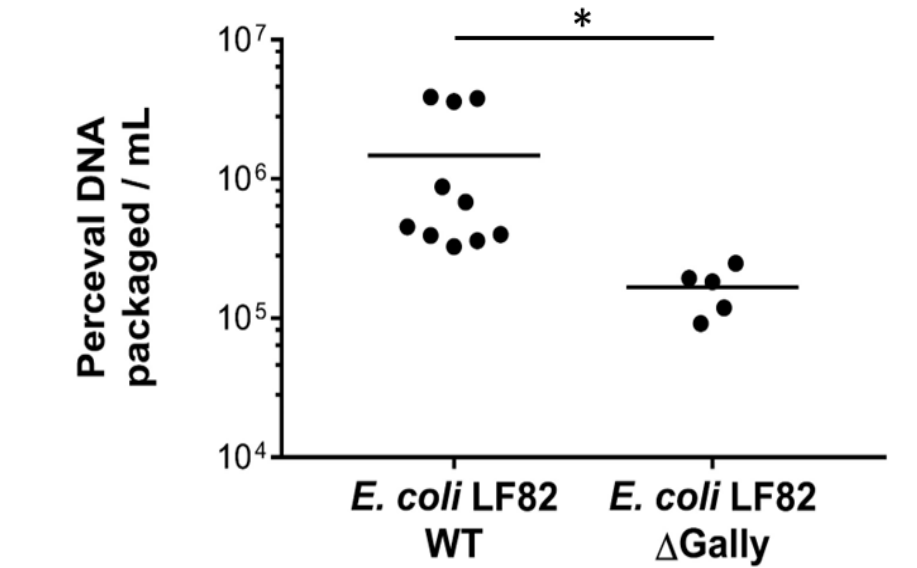
Toxin/Antitoxin systems ; Cold shock proteins ; Virulence

Important lateral transduction mediated by the pac type phage Gally

E. coli LF82 virome sequencing



Quantification of Perceval DNA packaged (qPCR)

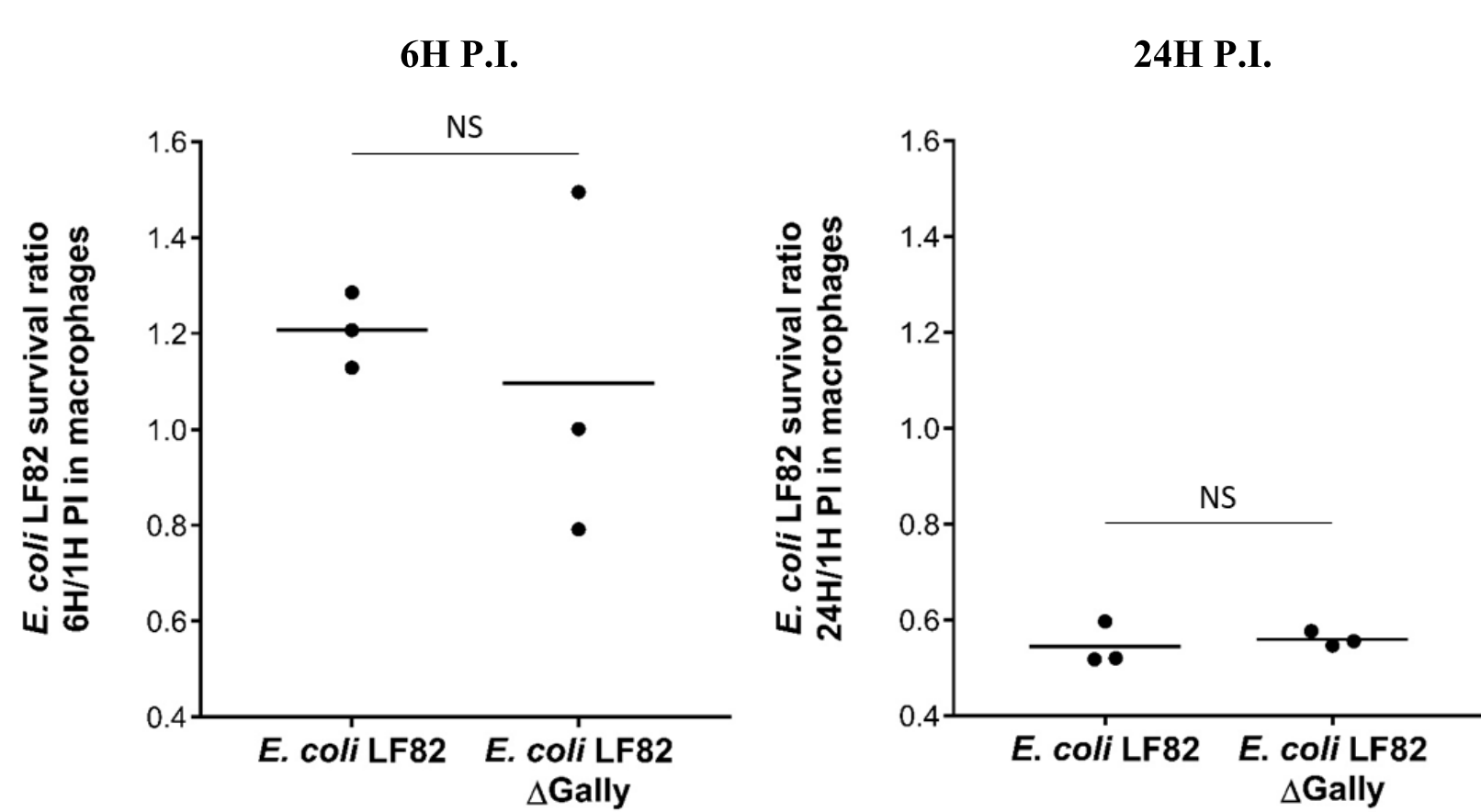


Gally transduces Perceval morons

- 90% of Perceval DNA packaged are contained in Gally virions
- Perceval carries morons (*emrE*, *sitABCD*)

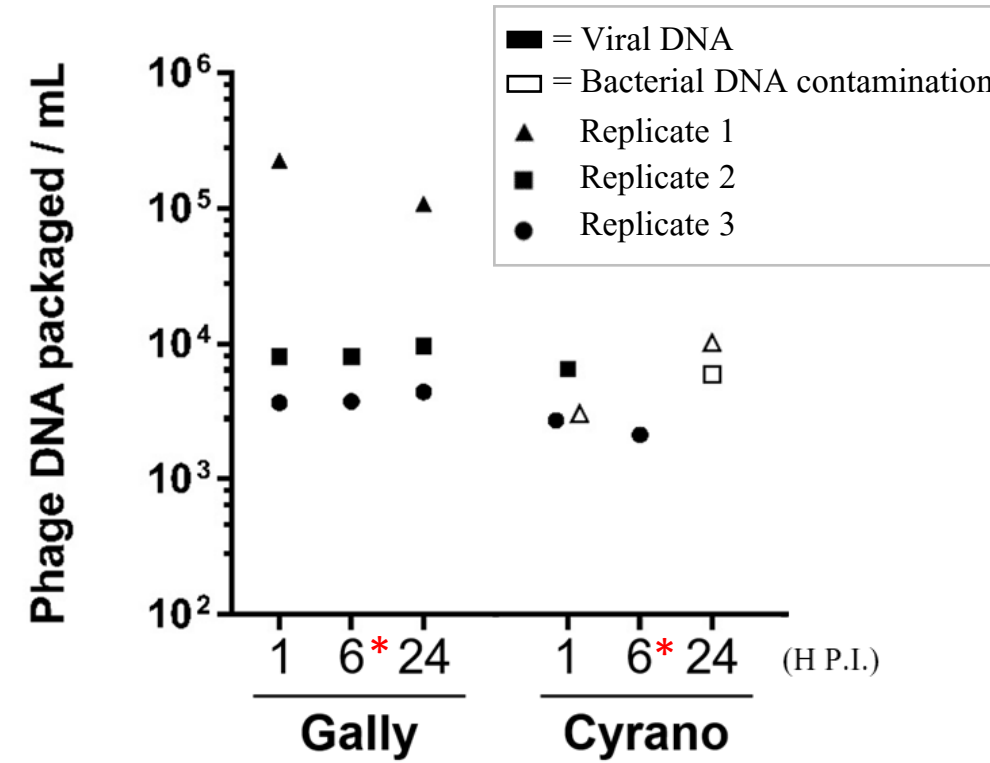
Prophage taming in macrophages

Gally has no impact on *E. coli* LF82 survival in macrophages



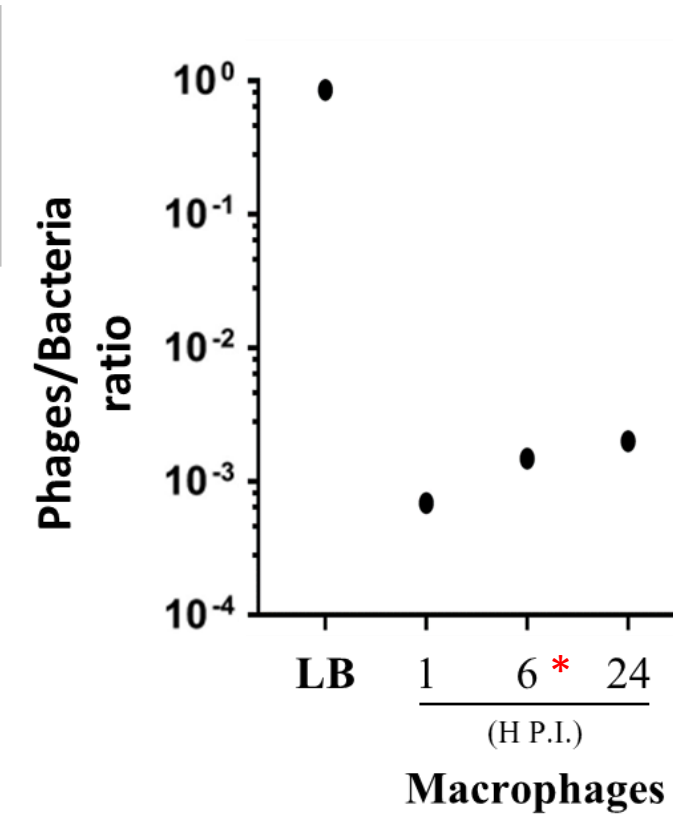
Gally and Cyrano inductions are repressed in macrophages

Quantification of phages produced in macrophages (qPCR)



* *E. coli* LF82 SOS-response in macrophages [3]

Gally phages / LF82 bacteria ratio

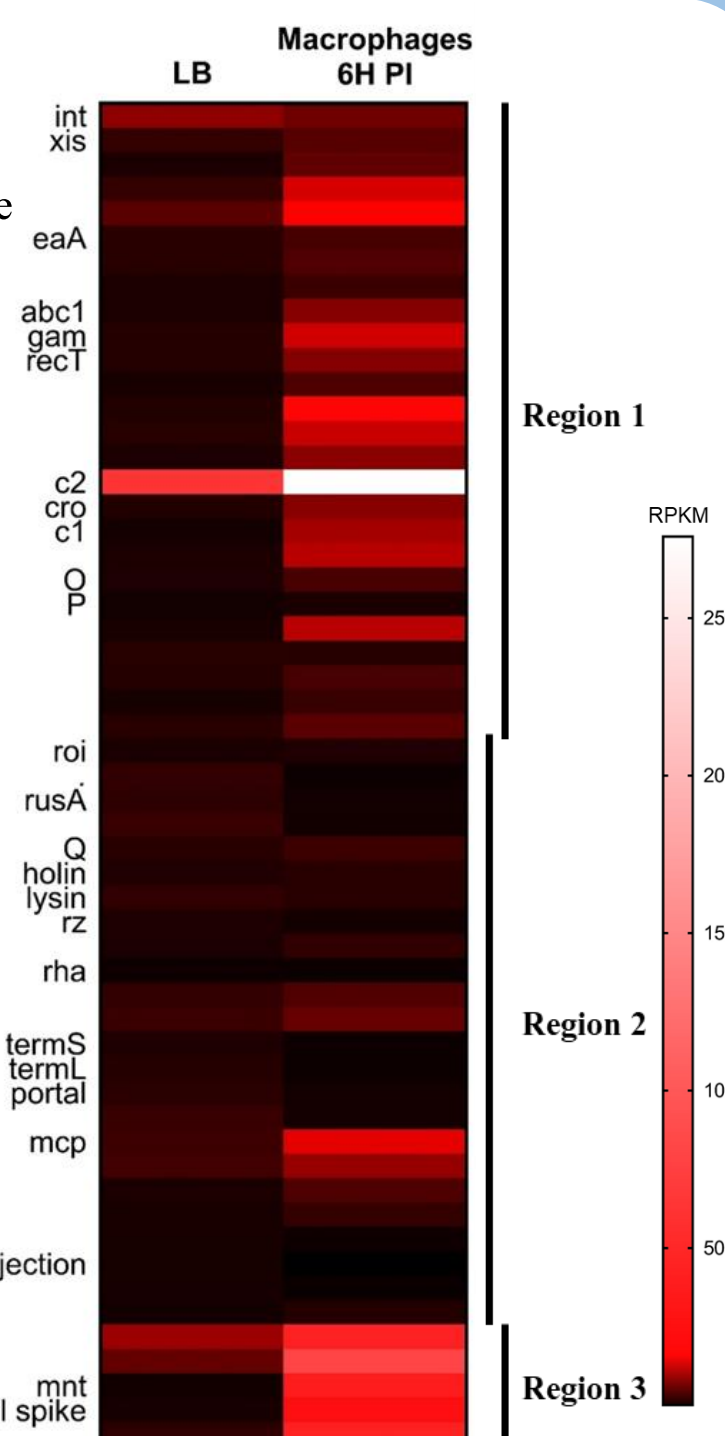


Transcriptomic analysis of Gally prophage

The Gally prophage induction seems to be partially repressed in macrophages

- Region 1 (+): replication module
- Region 2 (-): virion structure, packaging and lysis modules
- Region 3 (+): genes encoding 3 hypothetical proteins, Mnt repressor and one tail spike protein

(+): expressed in macrophages 6h PI
(-): repressed in macrophages 6h PI

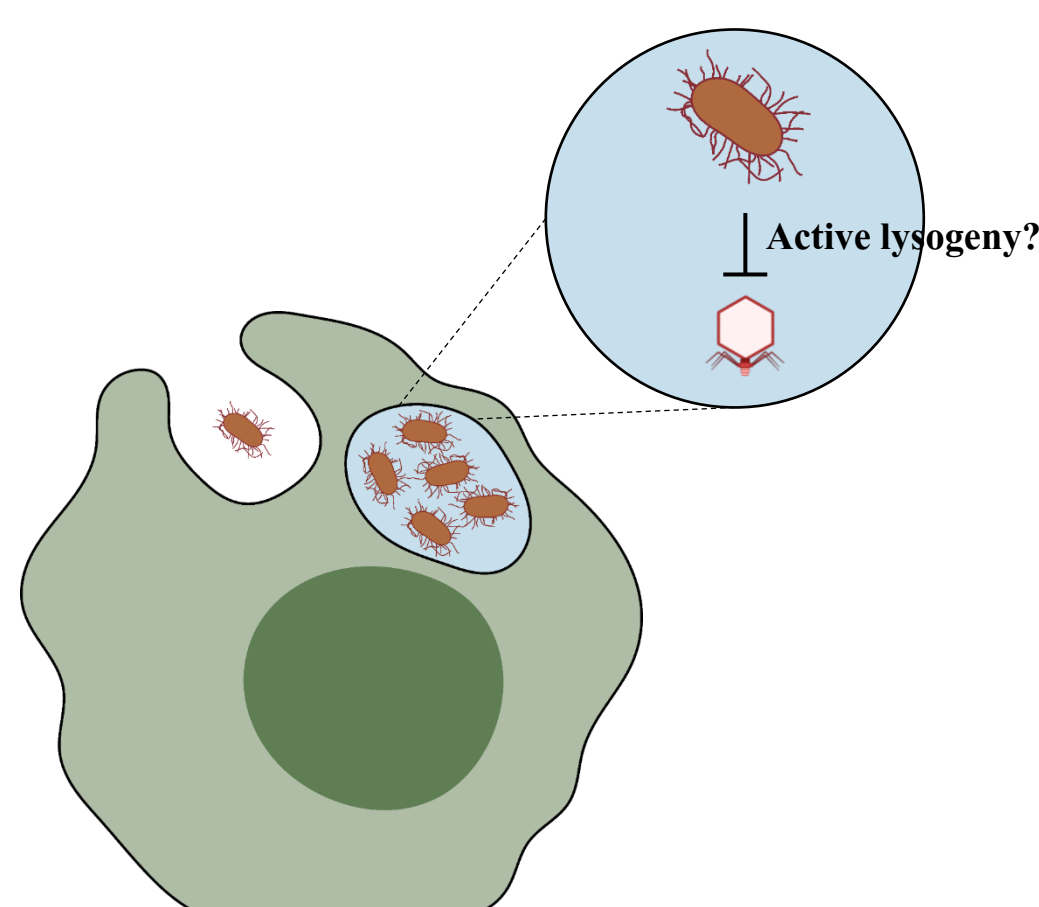


Conclusions

The 5 prophages of *E. coli* LF82 are active and form new virions.

Gally is the most abundant of them in *E. coli* LF82 virome. It is induced in presence of genotoxic stress and may be involved in the dispersal of LF82 virulence genes, thanks to its lateral transduction ability [3]. However, in macrophages, the Gally prophage induction is partially repressed in a manner similar to active lysogeny [5].

We hypothesize that this repression of the Gally phage cycle is the result of an adaptive mechanism of LF82 bacteria to regulate the expression of their most induced prophage upon macrophage infection. This may participate to its good survival in macrophages.



References

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- [2] Gilcrease E. and Casjens S. The Genome Sequence of Escherichia Coli Tailed Phage D6 and the Diversity of Enterobacteriales Circular Plasmid Prophages *Virology* 2018
- [2] Rakiitina DV., et al. Genome Analysis of *E. coli* isolated from Crohn's disease patients *BMC Genomics* 2017
- [3] Chen J., et al. Genome Hypermobility by Lateral Transduction *Science* 2018
- [4] Demarre G., et al. The Crohn's disease-associated *Escherichia coli* strain LF82 relies on SOS and stringent responses to survive, multiply and tolerate antibiotics within macrophages *PLoS Pathogens* 2019
- [5] Pasechnek A., et al. Active lysogeny in *Listeria monocytogenes* is a bacteria-phage adaptive response in the mammalian environment *Cell Reports* 2020