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Pauline Misson, Emma Bruder, Jeffrey K. Cornuault, Marianne De Paepe, Pierre Nicolas, et al..  
Phage production is blocked in the adherent-invasive Escherichia coli LF82 upon macrophage infection.  
Viruses Of Microbes 2023, Jul 2023, Tbilisi, Georgia. hal-04160179

**HAL Id: hal-04160179**

**<https://hal.science/hal-04160179>**

Submitted on 12 Jul 2023

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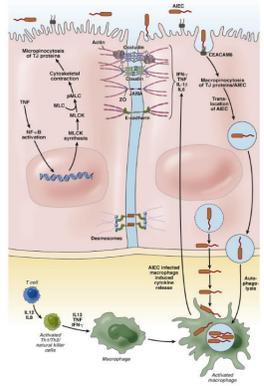
# Phage production is blocked in the adherent-invasive *Escherichia coli* LF82 upon macrophage infection

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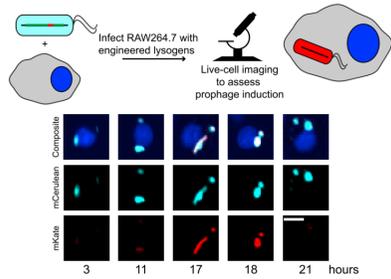
## Background and problematics

*Escherichia coli* LF82 is an adherent-invasive pathogen (AIEC) frequently found in the gut microbiota of patients with Crohn's disease (Darfeuille-Michaud et al. 1998)



- ✓ Adhesion to epithelial cells
- ✓ Invasion of underlying tissues
- ✓ Multiplication in macrophages despite multiple stresses (including ROS) (Demarre et al. *PLoS Pathogens* 2019)
- ✓ Increased inflammatory response, symptomatic of Crohn's disease

Shawki and McCole, *Cell Mol Gastroenterol Hepatol* 2017



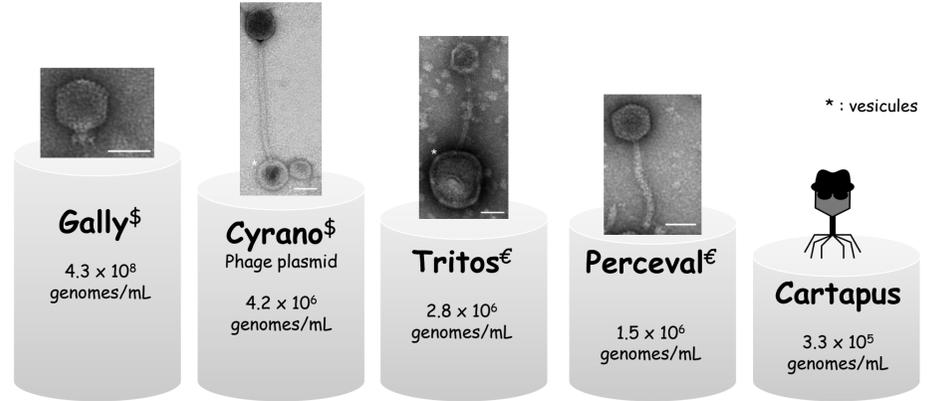
However, the macrophage is a genotoxic environment known to induce the lytic cycle of the phage lambda in a lysogenized *E. coli* MG1655 laboratory strain (Bodner et al. *Cell Syst* 2020).

- E. coli* LF82 hosts five predicted prophages (Miquel, et al. *PLoS ONE* 2010).
- Are these phages active under laboratory conditions?
  - Are they inducible by genotoxic stress?
  - Are they produced in macrophages?

How LF82 manage its prophages to survive in macrophages?

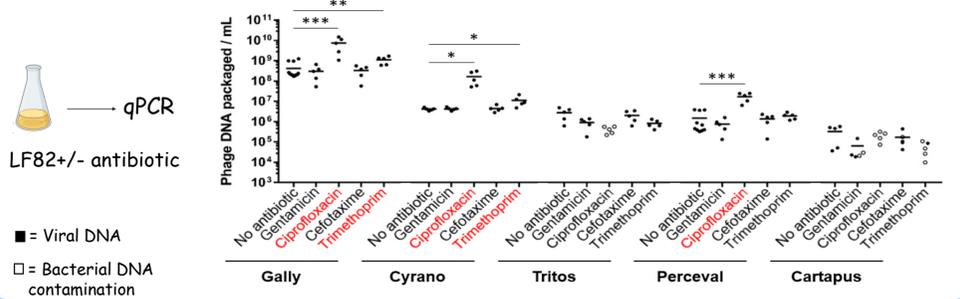
## The *Escherichia coli* LF82 virome

All five LF82 prophages are active under unstressed growth conditions



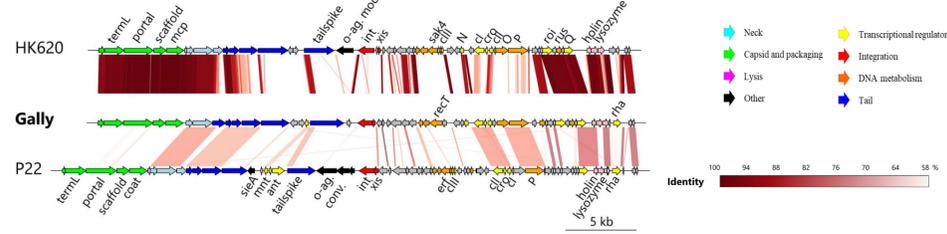
Electron microscopy images of LF82 culture supernatant (\$) or of purified phages produced by indicator strains (€)

Gally and Cyrano prophages are over-induced after genotoxic stress

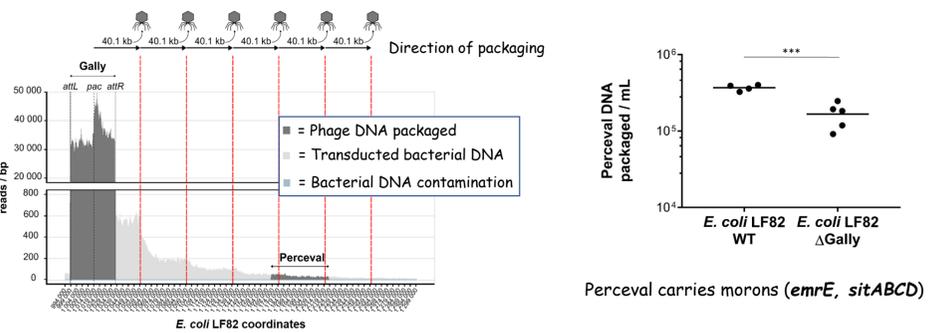


## Gally genome and cycle

### Genome organization

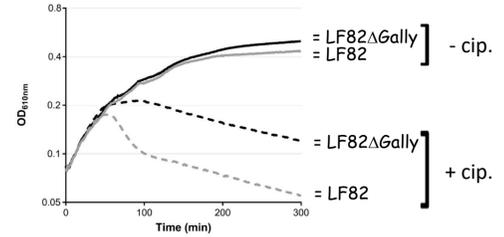
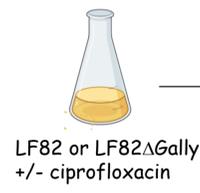


Gally mediates lateralized transduction, responsible for 50% of the perceval DNA encapsidation (DNA sequencing of the virome)

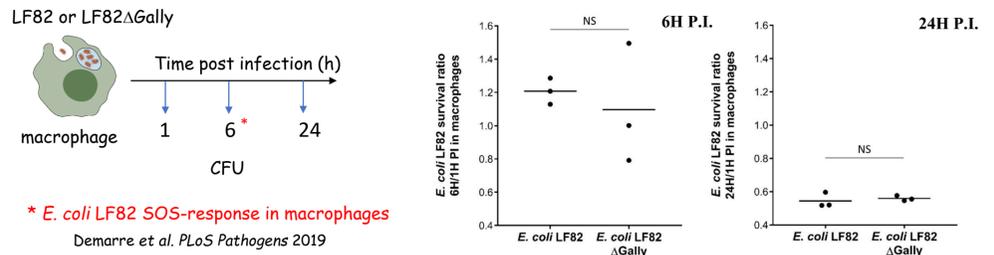


## Impact of Gally on LF82 survival

Gally is the main cause of bacterial lysis after a ciprofloxacin treatment...



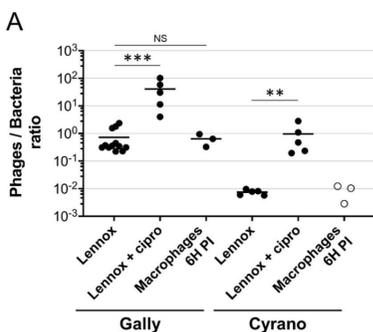
... but has no impact on LF82 viability in macrophages



## Phage production in macrophages

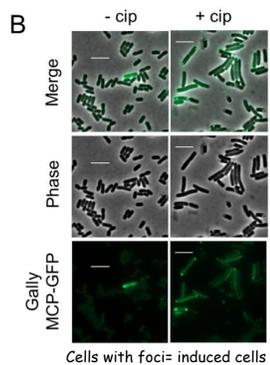
Gally and Perceval production are blocked in macrophages

Phage/bacteria ratio in different environments



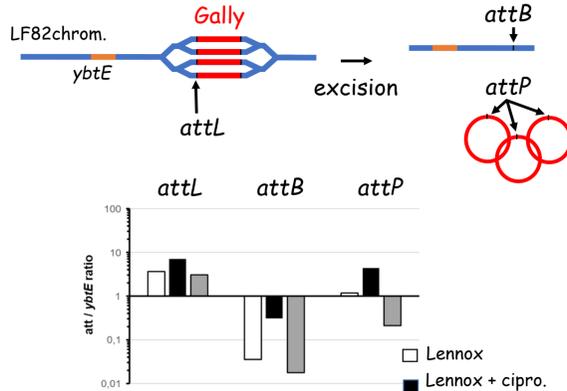
Gally & Cyrano production is similar in macrophages and under unstressed growth conditions

Gally MCP-GFP induction



Gally is induced in ~0.04% of LF82 in macrophages (0.37% or 44% *in vitro* in absence or presence of ciprofloxacin respectively)

Semi-quantification of attL (*in situ* replication marker), attP (replication after excision) and attB (excision) regions

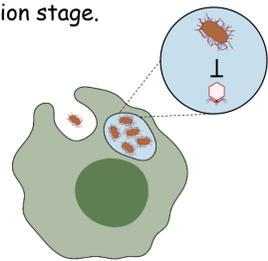


Gally excision and replication post-excision are decreased in macrophages, but not *in situ* replication

## Conclusion (Misson et al. *PLoS Pathogens* 2023)

Gally, the most produced prophage *in vitro* has no impact on LF82 viability in macrophages, due to repression of its lytic cycle at the excision stage.

We assume that Gally is finely regulated by LF82 to allow bacteria to survive in this genotoxic environment



What are the molecular determinants of this regulation?

Macrophage specific and dependent regulation?

Identification of transcriptional factors involved in this repression

