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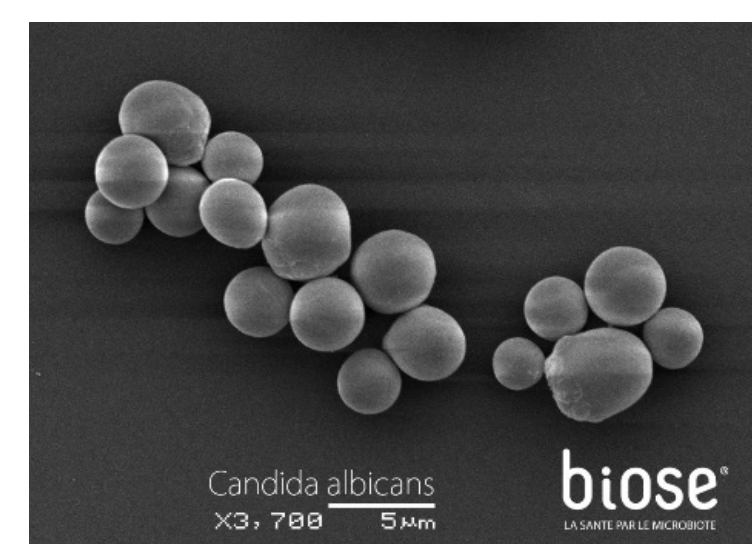
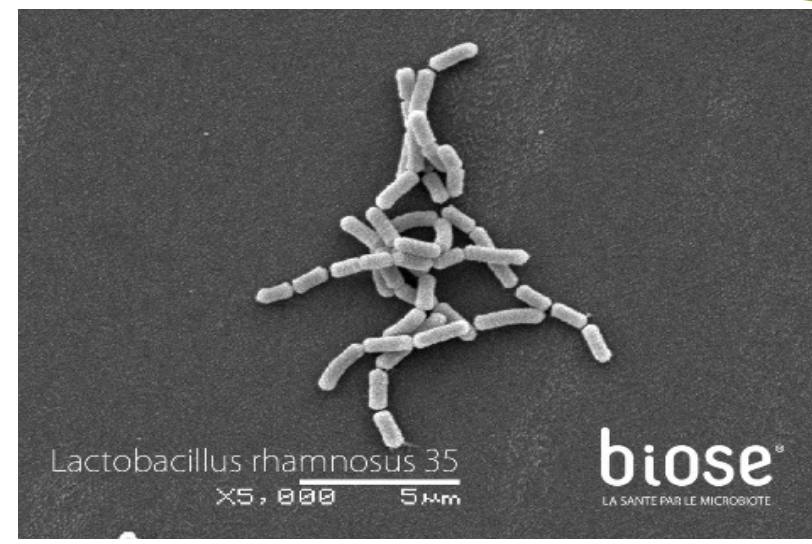
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In vivo study of probiotic and anti-*Candida albicans* properties of *Lactobacillus rhamnosus* Lcr35®

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Scientific background

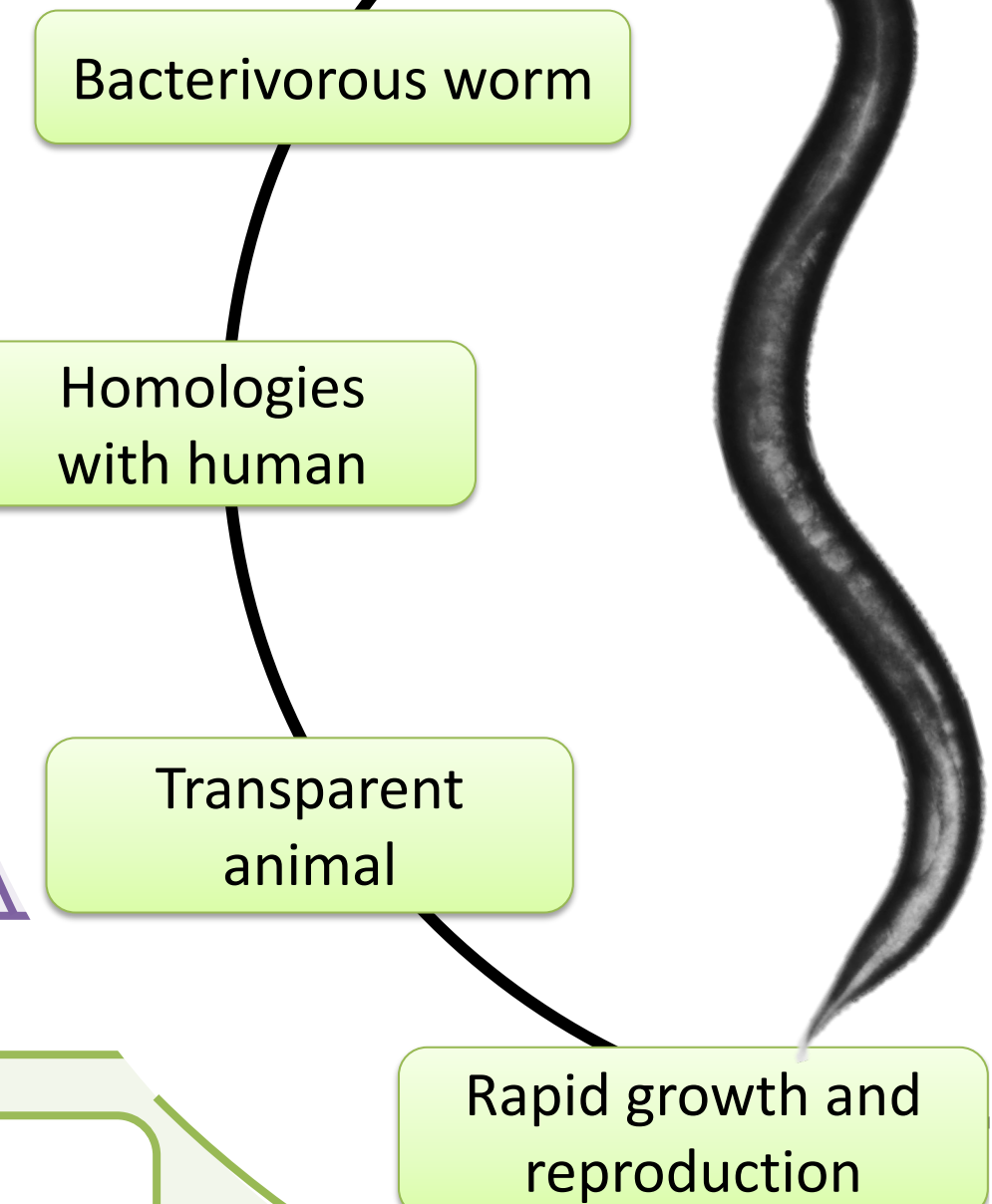
Proven probiotic effects of Lcr35®: anti-*Candida albicans* properties (opportunistic pathogenic yeast in humans) demonstrated by *in vitro* approaches [1] and clinical trials

→ molecular mechanisms not elucidated

in vivo mechanistic study

Caenorhabditis elegans, innovative animal model for studying microorganisms-microorganisms and microorganisms-host interactions

Why *C. elegans* ?



Methods

1- Physiological approaches

Prophylactic treatment:
Lcr35® 2 hours

Infection: *C. albicans* 2 hours

Curative treatment:
Infection: *C. albicans* 2 hours

Lcr35® 2 hours

Worm survival assay

Kaplan-Meier statistical model (log-rank test)

2- Targeted transcriptomic approach

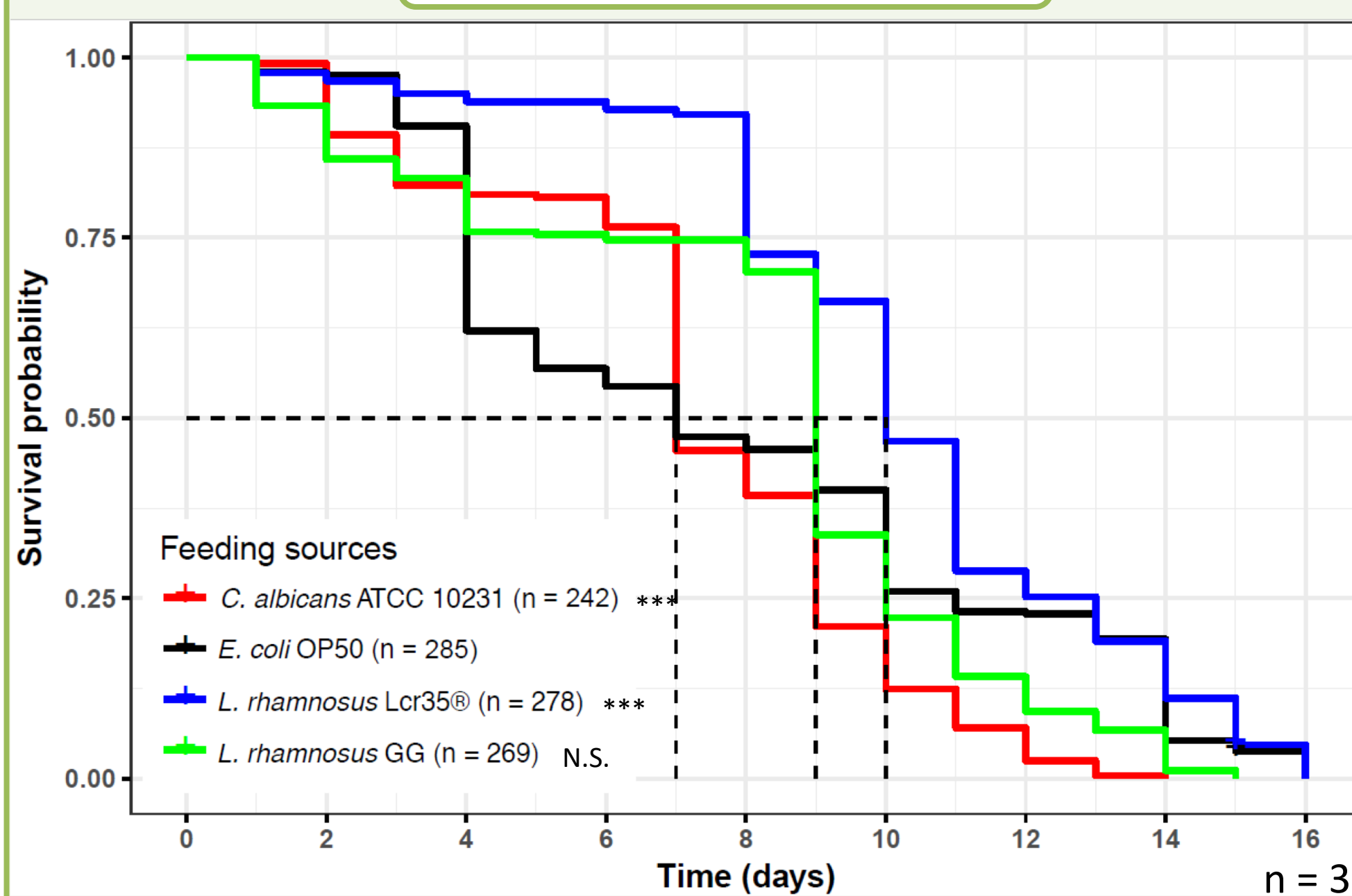
Quantification of gene expression by RT-qPCR at different times (2, 4, 6, 24 hours):

- lifespan: *daf-2* (insulin pathway)
- innate immunity: *sek-1* (p38 MAPK pathway)
- antimicrobial: *fipr-22/23*

$$E_{GOI} = \frac{(GOI \text{ efficiency})^{\Delta Ct_{GOI}}}{\sqrt{(cdc-42 \text{ efficiency})^{\Delta Ct_{cdc-42}} \times (Y45F10D.4 \text{ efficiency})^{\Delta Ct_{Y45F10D.4}}}}$$

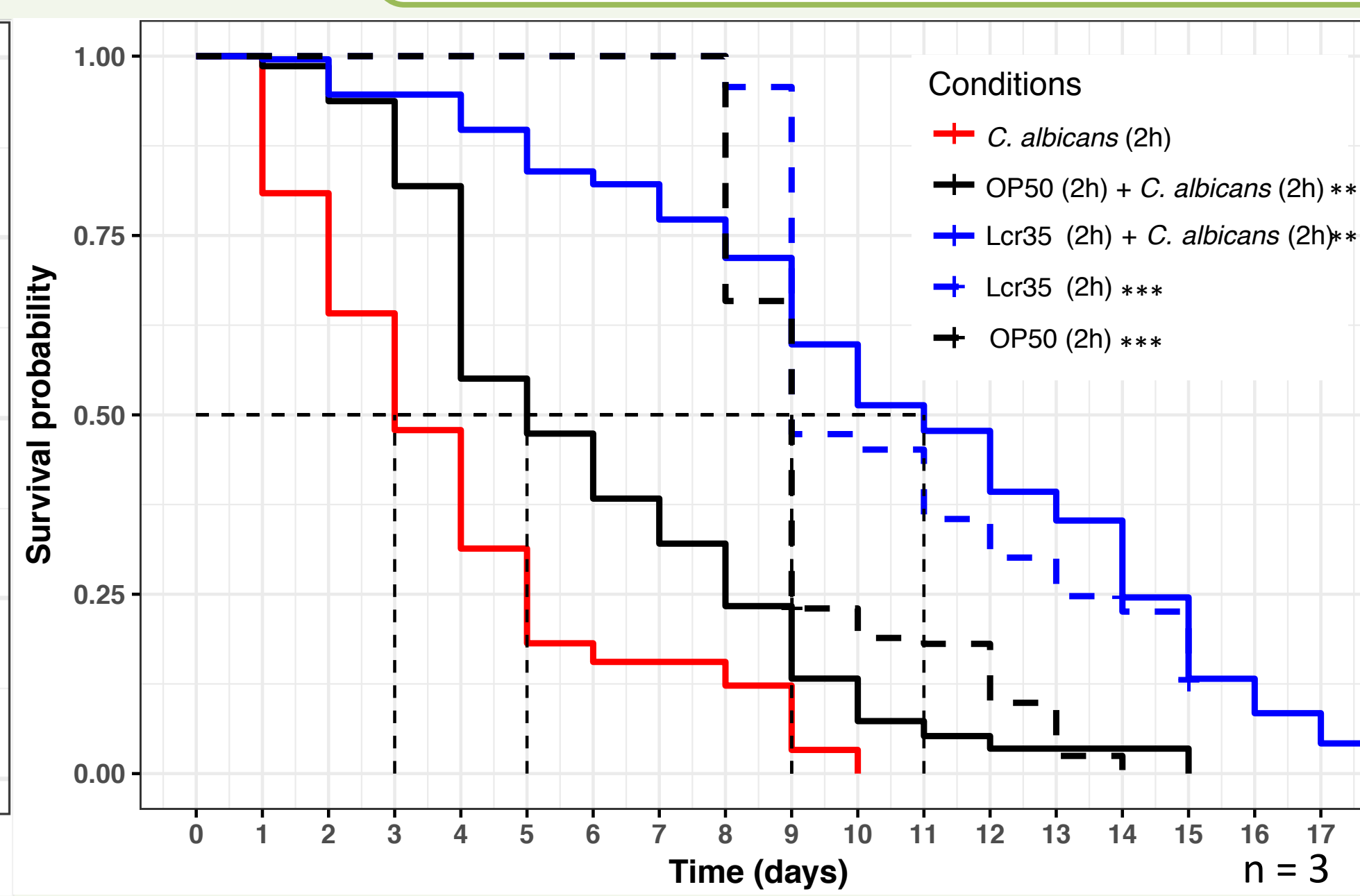
Results

C. elegans lifespan assay

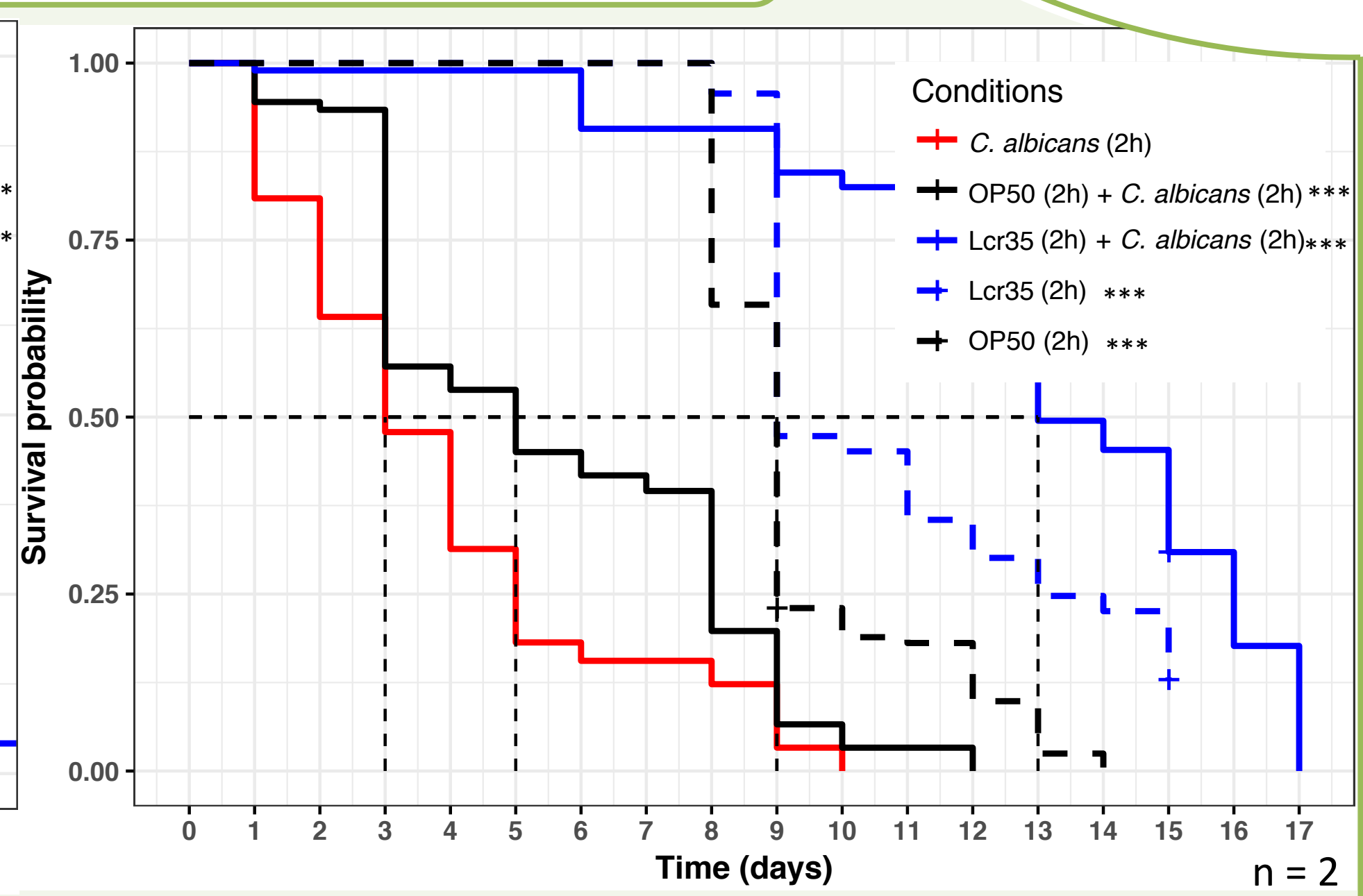


C. albicans : pathogenic (mean lifespan reduced to 7 d)
Lcr35® : beneficial strain (mean lifespan increased to 10 d)

Experimental candidiasis in *C. elegans* : survival assay with a prophylactic ... or a curative treatment

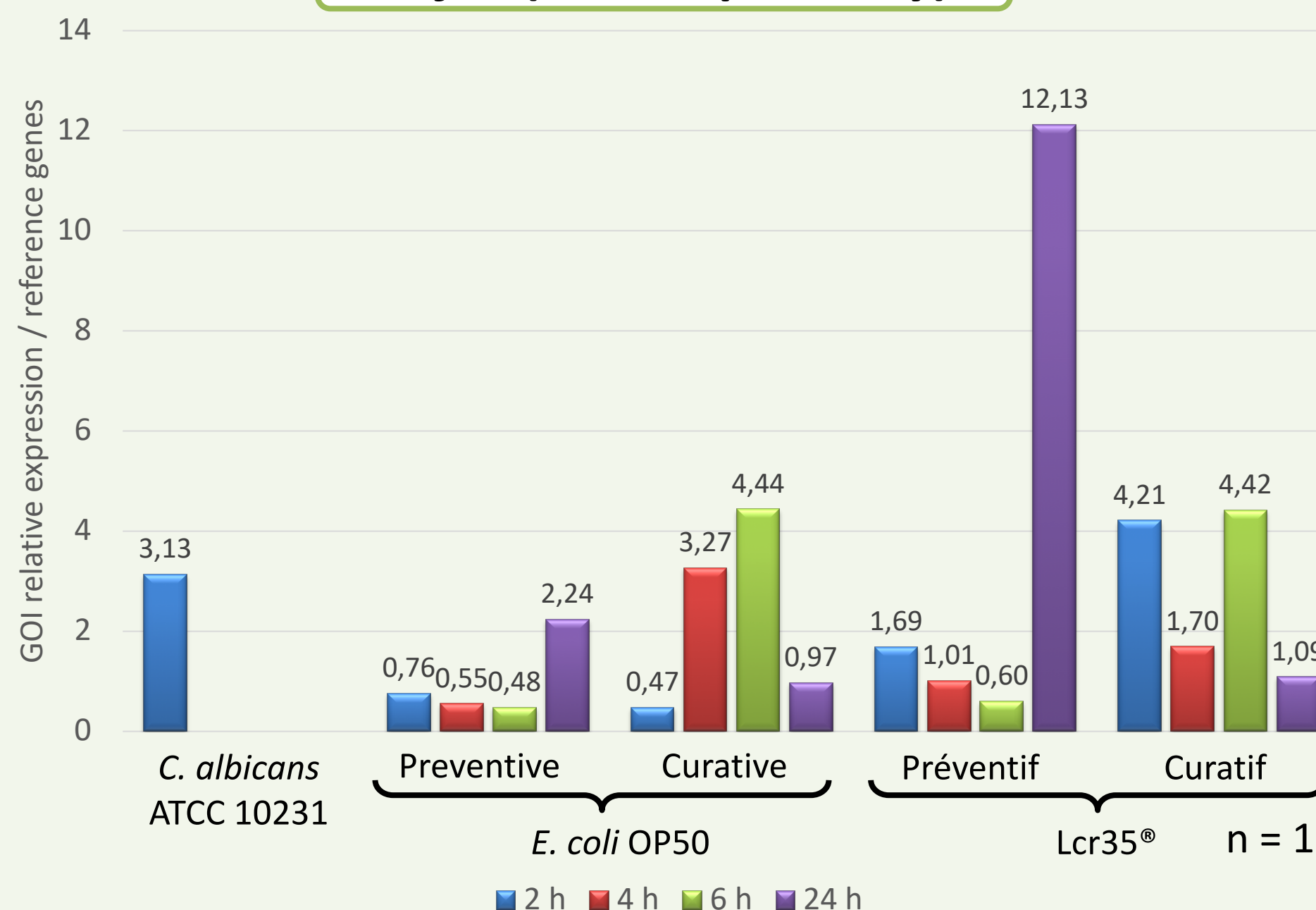


Candida albicans: mean lifespan of 3 d
Lcr35® + *C. albicans*: mean lifespan of 11 d (+ 267 %)
Lcr35® has a preventive effect against *C. albicans*



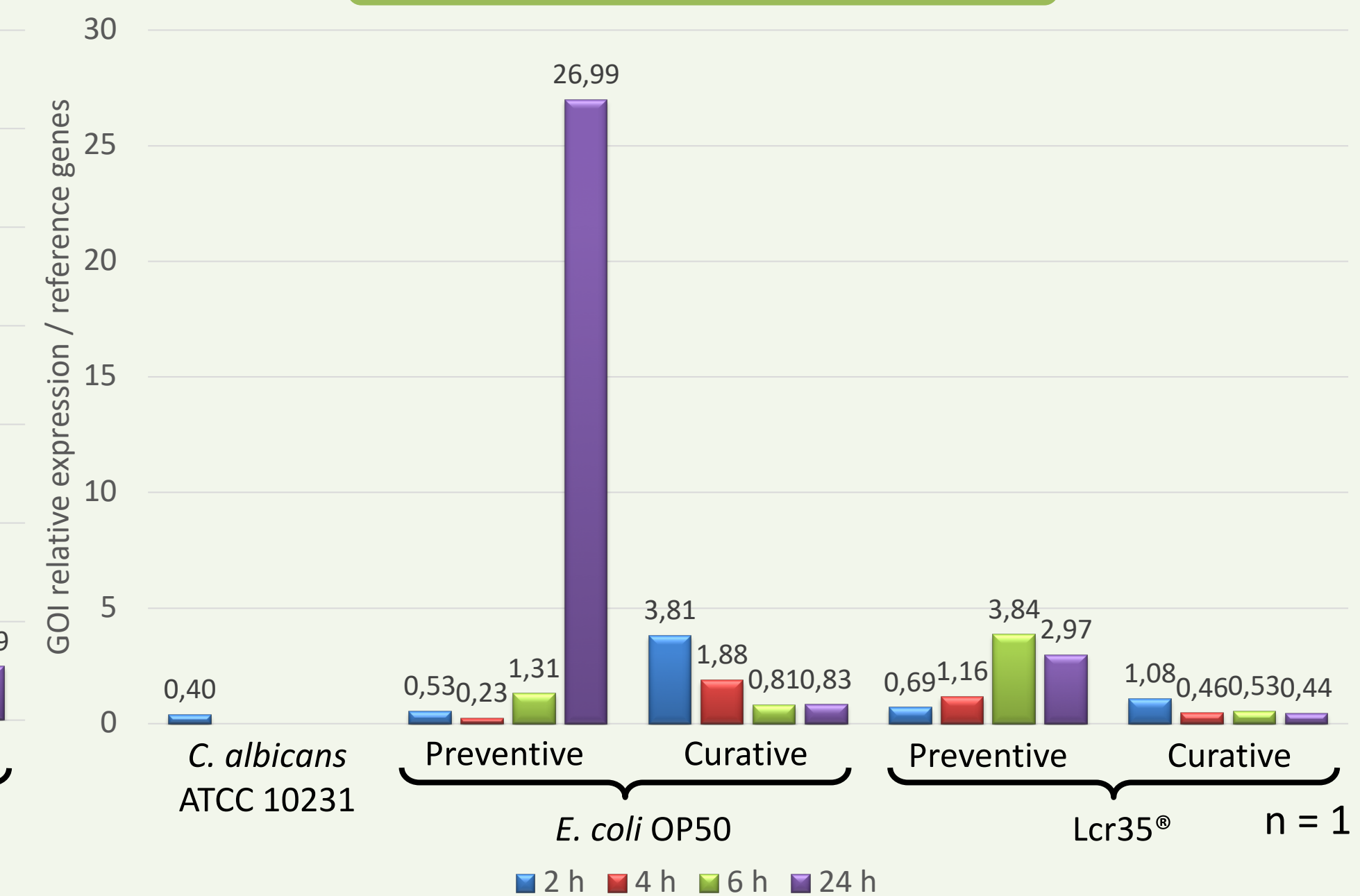
Candida albicans: mean lifespan 3 d
C. albicans + Lcr35®: mean lifespan of 13 d (+ 333 %)
Lcr35® has a curative effect against *C. albicans*

daf-2 (insulin pathway)



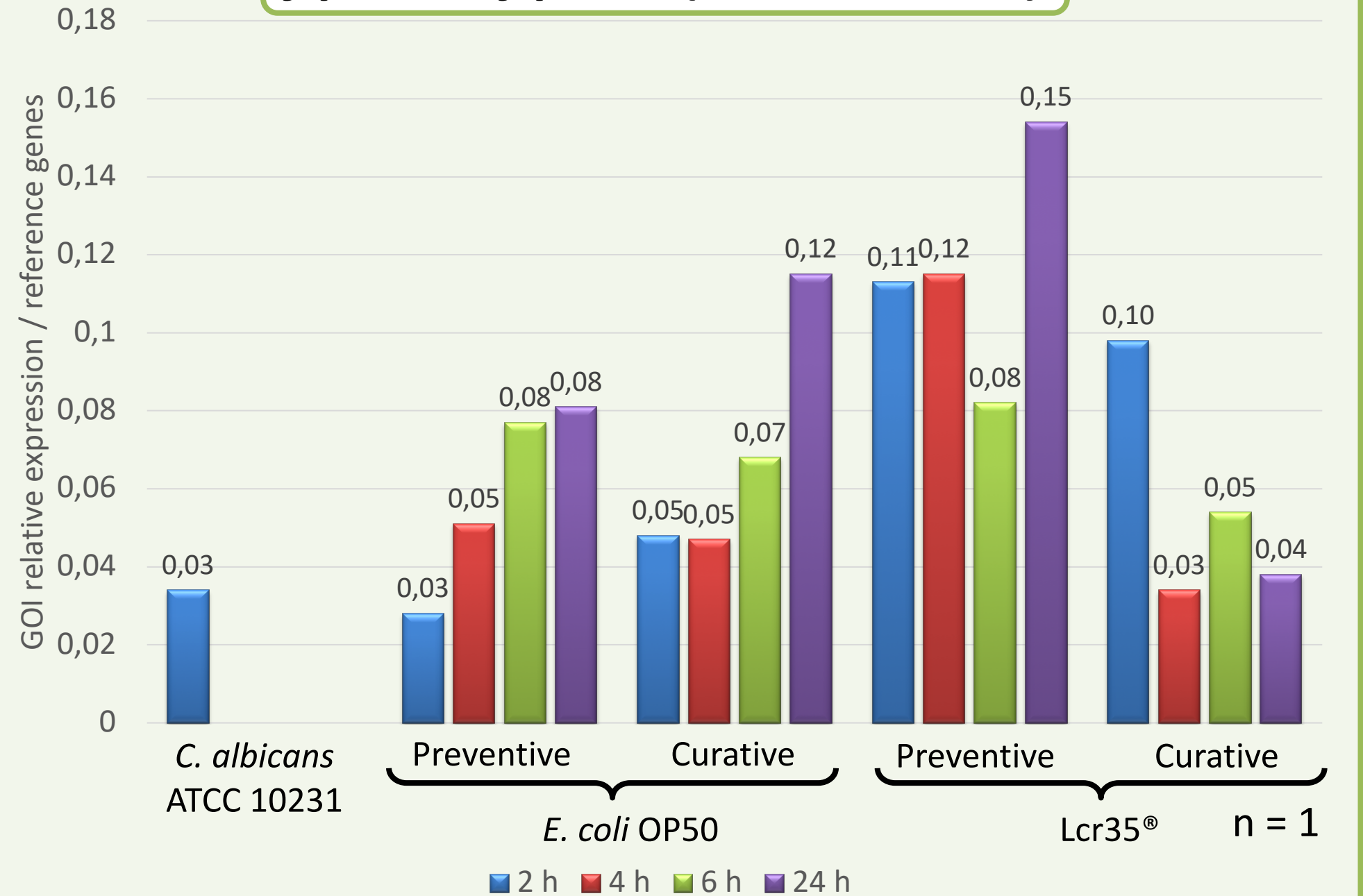
OP50: underexpression
Lcr35® (preventive): under- then late overexpression (t = 4h)
Lcr35® (curative): few effects or underexpression

sek-1 (p38 MAPK pathway)



OP50: overexpression (⤴ in preventive; ⤵ in curative)
Lcr35® (preventive): overexpression
Lcr35® (curative): early overexpression (t = 2h) then no effects

fipr-22 / fipr-23 (antimicrobial)



OP50: late overexpression (t = 24h)
Lcr35® (preventive): early and stable overexpression
Lcr35® (curatif): early (t = 2h) but temporary overexpression

Conclusion

- Significant protective effects of Lcr35® on *Caenorhabditis elegans* :
 - ✓ Inhibition by Lcr35® of *Candida albicans* effects on *C. elegans* survival
 - ✓ Effective preventive and curative treatments
- Preliminary results compared to *C. albicans* ATCC 10231:
 - ✓ In preventive, overexpression of genes involved in immunity (*sek-1*, *fipr-22/23*), underexpression of the gene involved in longevity (*daf-2*) (except at t = 24 h) in the presence of Lcr35®
 - ✓ In curative, similar expression of GOIs in the presence of Lcr35®

References

- [1] Nivoliez A et al. (2012) Influence of manufacturing processes on *in vitro* properties of the probiotic strain *Lactobacillus rhamnosus* Lcr35®. J Biotechnol 160:236–241.
[2] de Barros PP et al. (2018) *Lactobacillus paracasei* 28.4 reduces *in vitro* hyphae formation of *Candida albicans* and prevents the filamentation in an experimental model of *Caenorhabditis elegans*. Microb Pathog 117:80–87.

Perspectives

- Monitoring the colonization of the worm intestine by the probiotic and the pathogen
- Identification of *C. elegans* signaling pathways modulated by Lcr35® by RNA sequencing followed by a metabolomic study

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