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**Curative treatment of candidiasis by the live  
biotherapeutic microorganism *Lactobacillus rhamnosus*  
Lcr35® in the invertebrate model *Caenorhabditis*  
*elegans*: first mechanistic insights**

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# Curative treatment of candidiasis by the live biotherapeutic microorganism *Lactobacillus rhamnosus* Lcr35<sup>®</sup> in the invertebrate model *Caenorhabditis elegans*: first mechanistic insights

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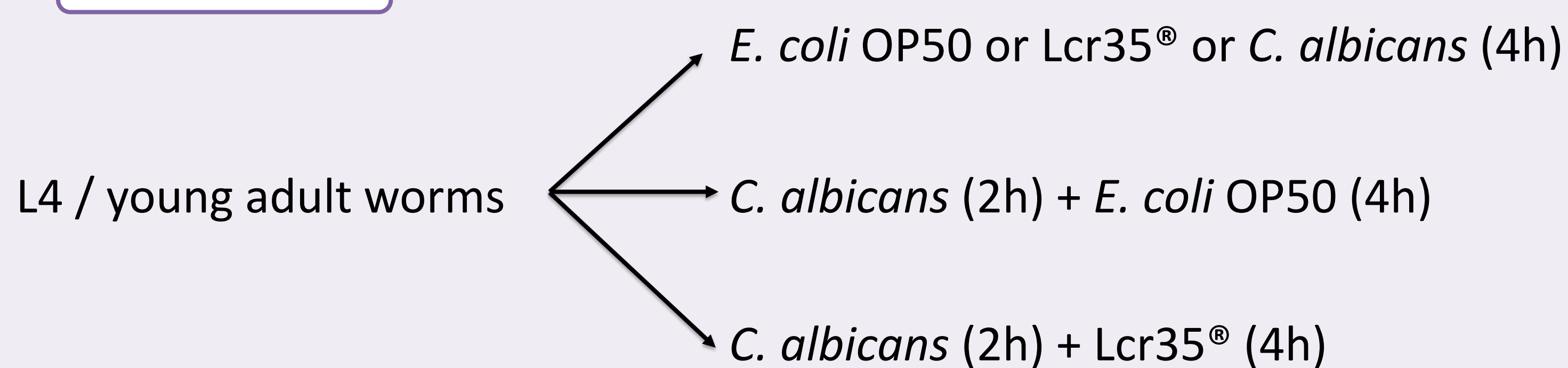
## Scientific background

Proven probiotic effects of Lcr35<sup>®</sup>: anti-*Candida albicans* (opportunistic pathogenic yeast in humans) properties demonstrated by *in vitro* approaches [1], clinical trials and by an *in vivo* preventive approach [2]  
→ **molecular mechanisms not elucidated**

*in vivo*  
mechanistic study

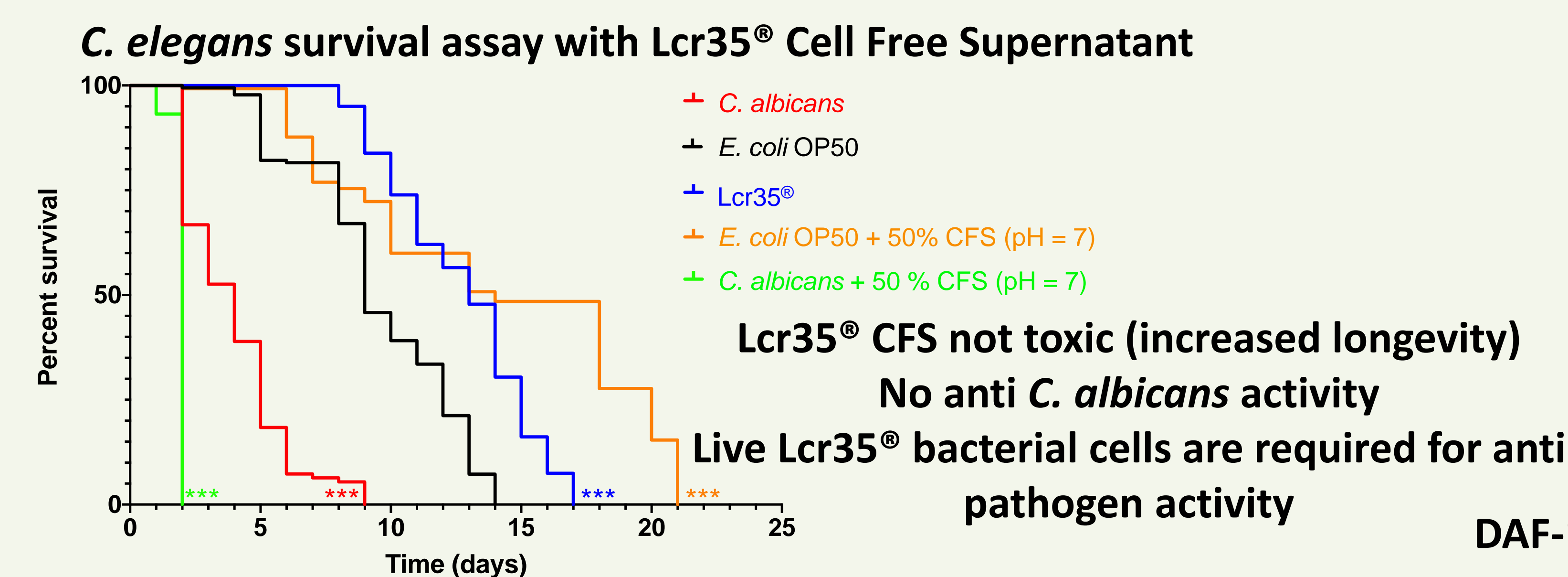
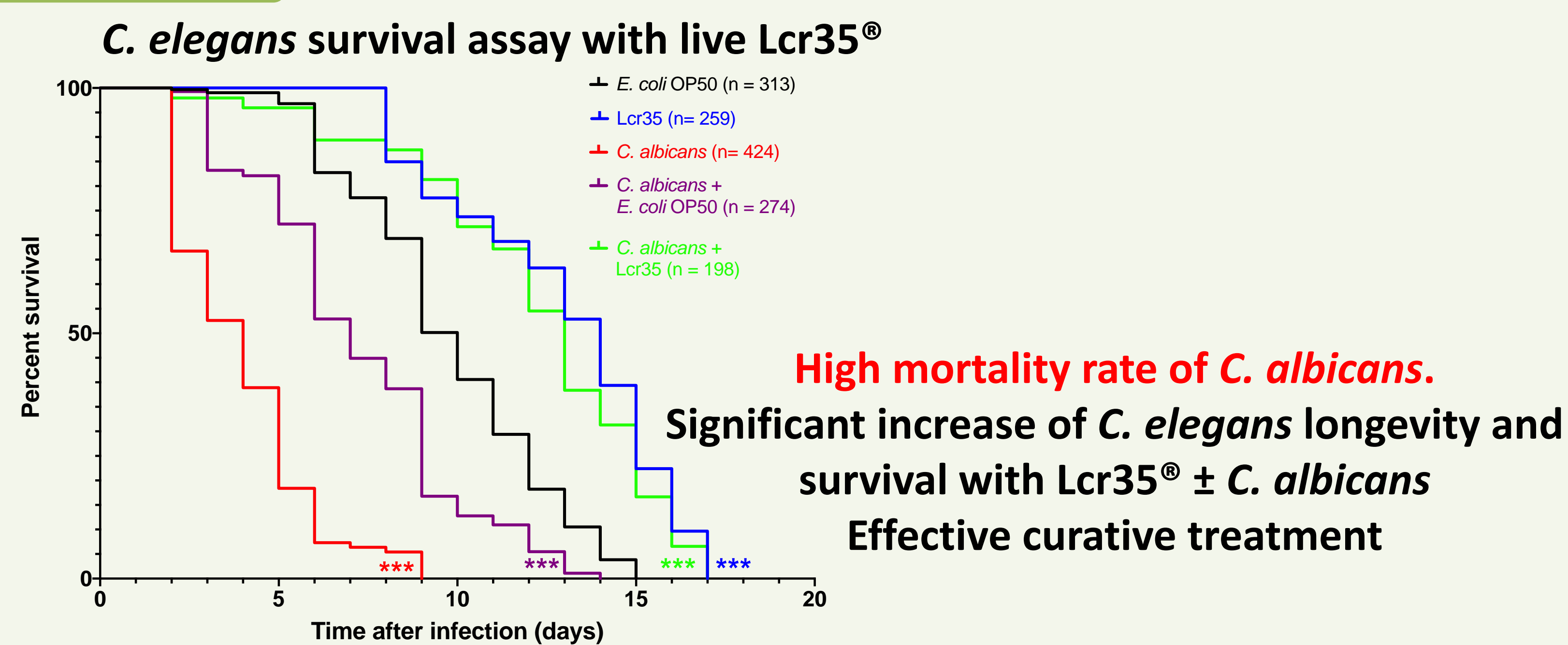
*Caenorhabditis elegans*, innovative animal model for studying microorganisms-microorganisms and microorganisms-host interactions  
Pertinent model between *in vitro* and *in vivo* models using mammals.

## Methods

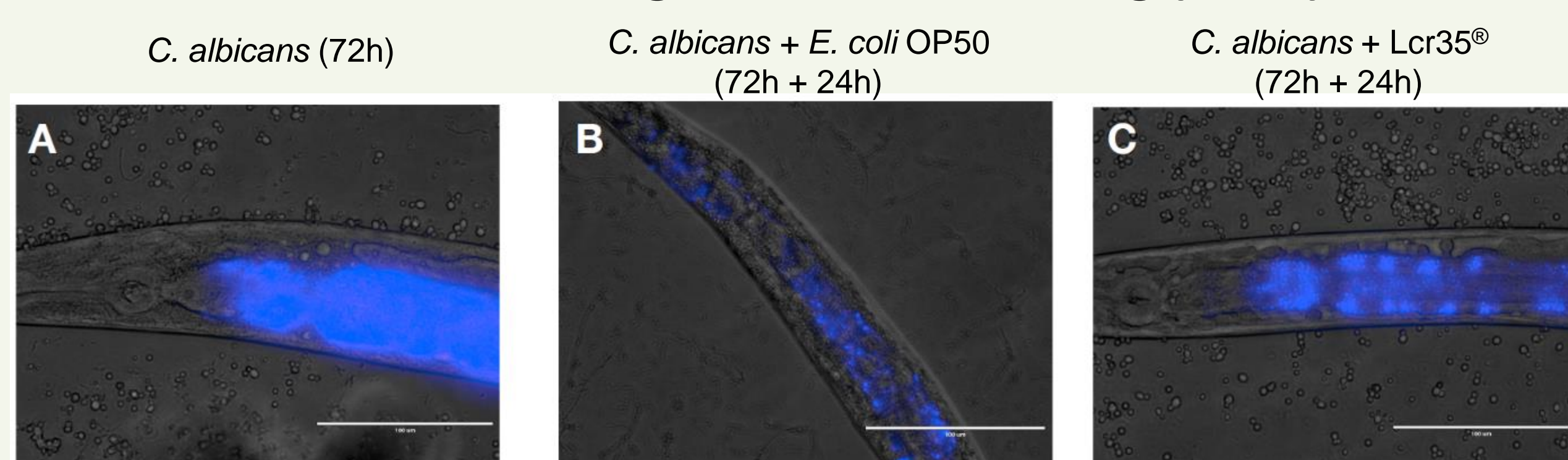


- *C. elegans* survival assay
- Determination of *C. elegans* DAF-16 cellular localization
- *C. elegans* transcriptomic assay
- Evaluation of the presence of *C. albicans* in the worm's gut

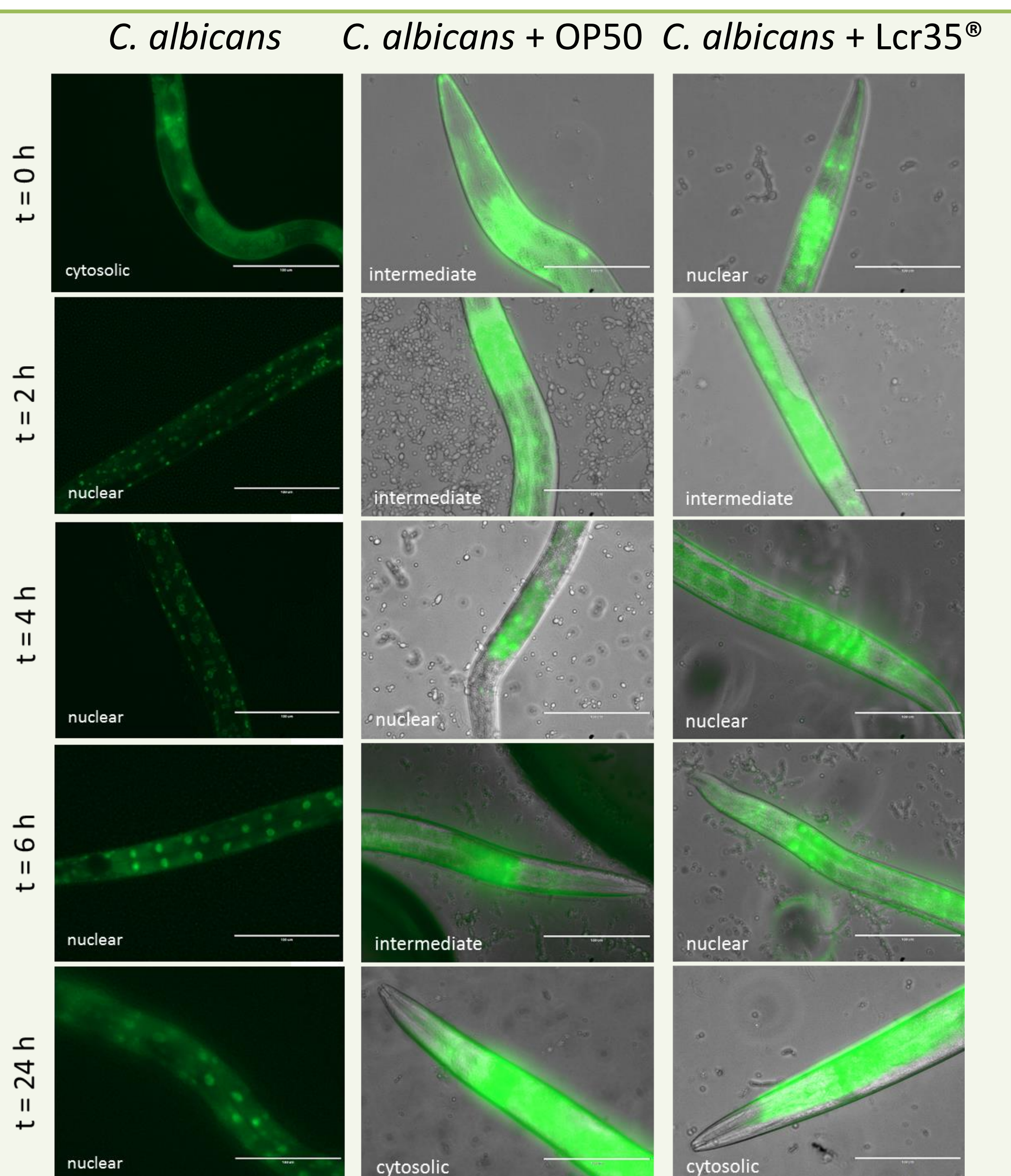
## Results



### Gut colonizing *C. albicans* staining (DAPI)



Presence of the yeast in each conditions. A curative treatment does not allow the elimination of the pathogen



**DAF-16 activity: activation of the transcription factor during a curative treatment**

Conditions	Genes of interest relative expression						
	Insulin-like pathway	p38 MAPK pathway		Antimicrobials			
	<i>daf-2</i>	<i>daf-16</i>	<i>sek-1</i>	<i>pmk-1</i>	<i>abf-2</i>	<i>cnc-4</i>	<i>fipr-22 / fipr-23</i>
Lcr35 <sup>®</sup>		5.84 ***	0.50	3.05		8.48	
<i>C. albicans</i>		0.31	4.57	4.66	3.58	14.31	3.45
<i>C. albicans</i> + <i>E. coli</i> OP50		0.41		2.57		7.04	0.26
<i>C. albicans</i> + Lcr35 <sup>®</sup>			11.24 **	2.42	8.00 **		4.29 *

**Lcr35<sup>®</sup> as a curative treatment induced an upregulation of p38 MAPK and antimicrobials encoding genes**

## Conclusion

- This is the unique study using the *C. elegans* model for deciphering the molecular mechanisms of a candidiasis curative treatment.
- Lcr35<sup>®</sup> protects the animal from the fungal infection (+225% of survival,  $p < 2 \times 10^{-16}$ ) even if the yeast is detectable in its intestine. In contrast, the Lcr35<sup>®</sup> cell-free supernatant does not appear to have any antipathogenic effect. At the mechanistic level, the DAF-16/Forkhead Box O transcription factor is activated by Lcr35<sup>®</sup> and genes of the p38 MAP Kinase signaling pathway and genes involved in the antifungal response are upregulated in presence of Lcr35<sup>®</sup> after *C. albicans* infection.
- These results suggest that the probiotic strain acts by stimulating its host *via* DAF-16 and the p38 MAPK pathway.

## References

- [1] Nivoliez A et al. (2012) Influence of manufacturing processes on *in vitro* properties of the probiotic strain *Lactobacillus rhamnosus* Lcr35<sup>®</sup>. J Biotechnol
- [2] Poupet C et al. (2019) *Lactobacillus rhamnosus* Lcr35 as an effective treatment for preventing *Candida albicans* infection in the invertebrate model *Caenorhabditis elegans*: First mechanistic insights. PLoS One
- [3] Poupet C et al. (2019) "Curative Treatment of Candidiasis by the Live Biotherapeutic Microorganism *Lactobacillus rhamnosus* Lcr35<sup>®</sup> in the Invertebrate Model *Caenorhabditis elegans*: First Mechanistic Insights," *Microorg.*

## Scientific outlook

- Global transcriptomic study on *C. elegans* by RNA sequencing
- Study of the modulation of virulence genes in *C. albicans*
- Characterization of metabolites involved in host-microorganism interactions by metabolomics
- Study of the strain-dependent aspect of the results by testing other probiotic / pathogenic couples

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