Lactobacillus rhamnosus Lcr35® as an effective treatment for preventing Candida albicans infection in the preclinical model Caenorhabditis elegans

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2 Biose Industrie

VerMidi XXII – Sorbonne University

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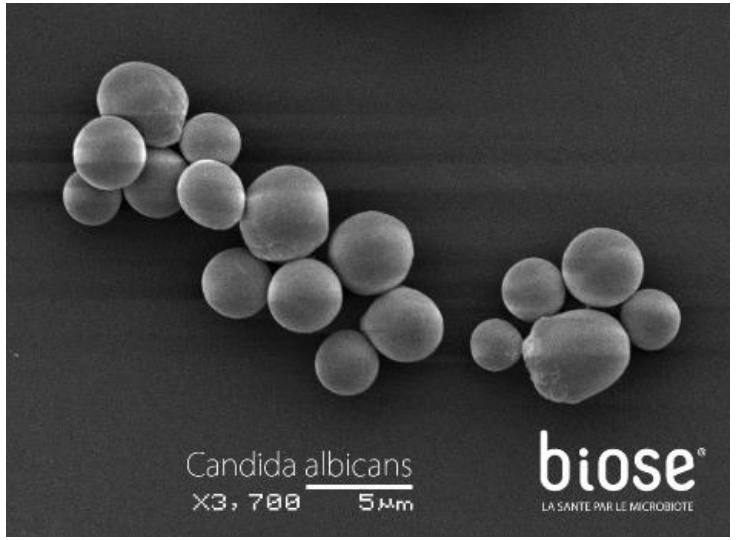
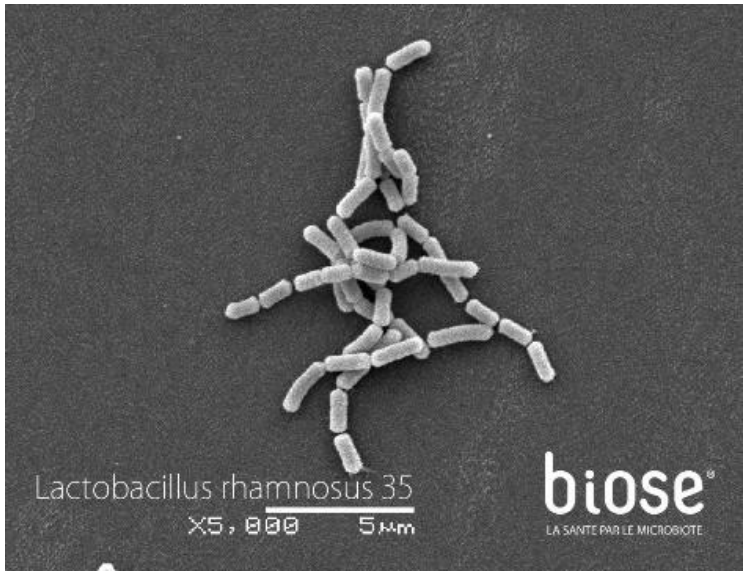
Scientific context



***Candida albicans* ATCC 10231**

- Opportunistic pathogen yeast
- Intestinal and vaginal candidiasis
- Concerns 75% of women worldwide

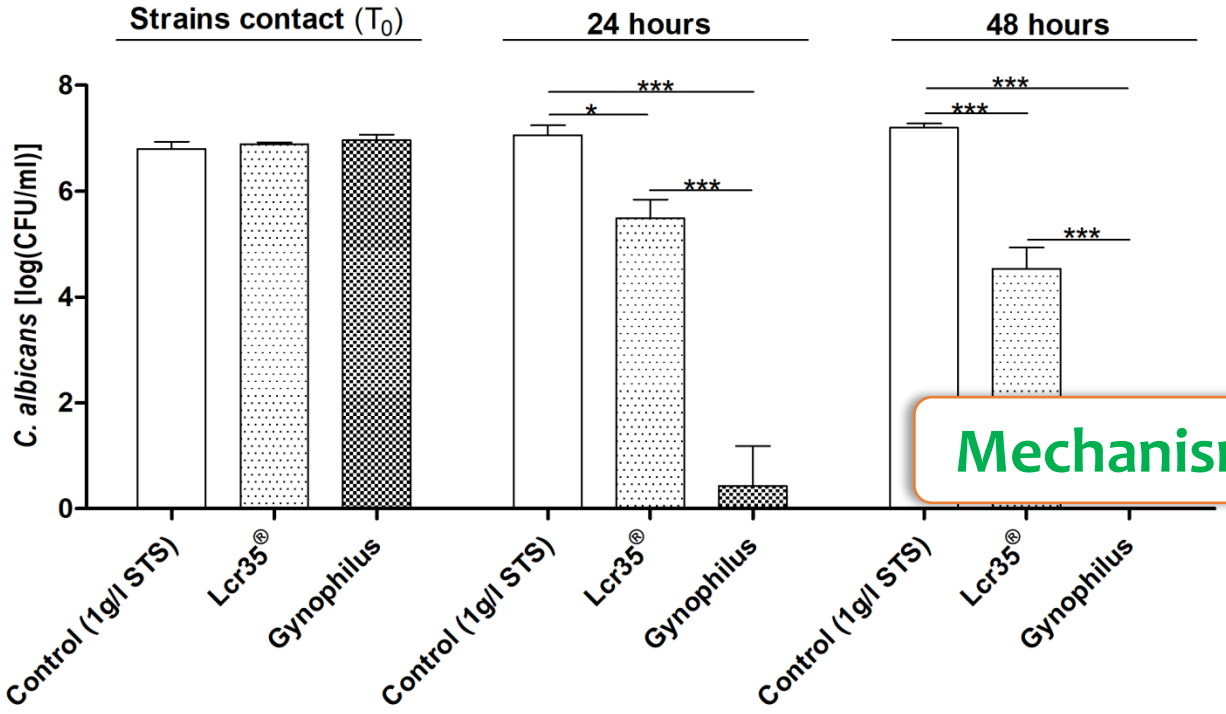
Anti-pathogen



***Lactobacillus rhamnosus* Lcr35®**

- Lactic acid bacterium
- Marketed by biose®
- Probiotic properties
- Therapeutic applications (intestinal and vaginal)

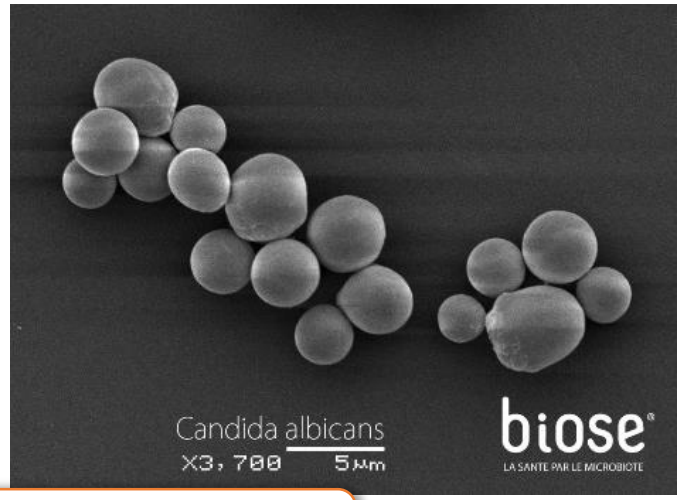
Scientific context



Monitoring of *C. albicans* ATCC 10231 count in co-culture with Lcr35®

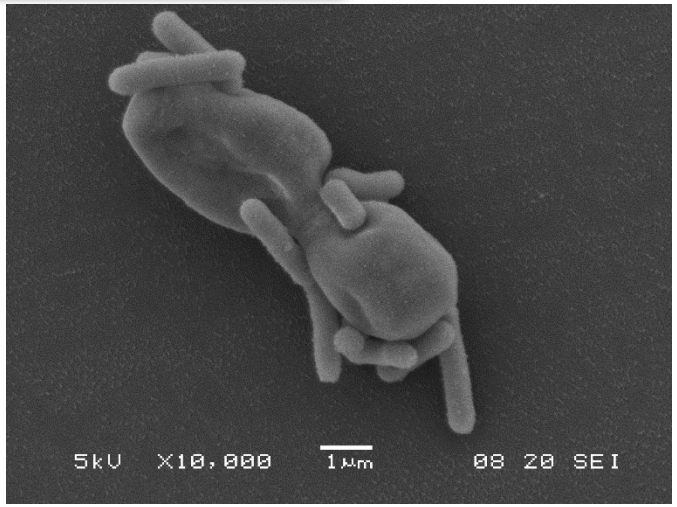
Nivoliez *et al.* 2012

Anova test with bonferroni correction
* $p < 0,05$; ** $p < 0,01$; *** $p < 0,001$



***C. albicans* without Lcr35®**

Mechanism of action?



***C. albicans* in presence of Lcr35®**

Dausset et al.
personnal communication

Aim & issues of the project

Understanding the molecular mechanisms involved in Lcr35® probiotic effects

In vivo approach

A LBP:

1) contains **live microorganisms,**
2) is applicable to the **prevention, treatment,** or **cure** of a disease
3) is **not a vaccine.**

Identifying the genes and molecules enabling Lcr35® anti-*Candida albicans* effects

Developing new Live Biotherapeutic Products (LBPs) containing Lcr35®

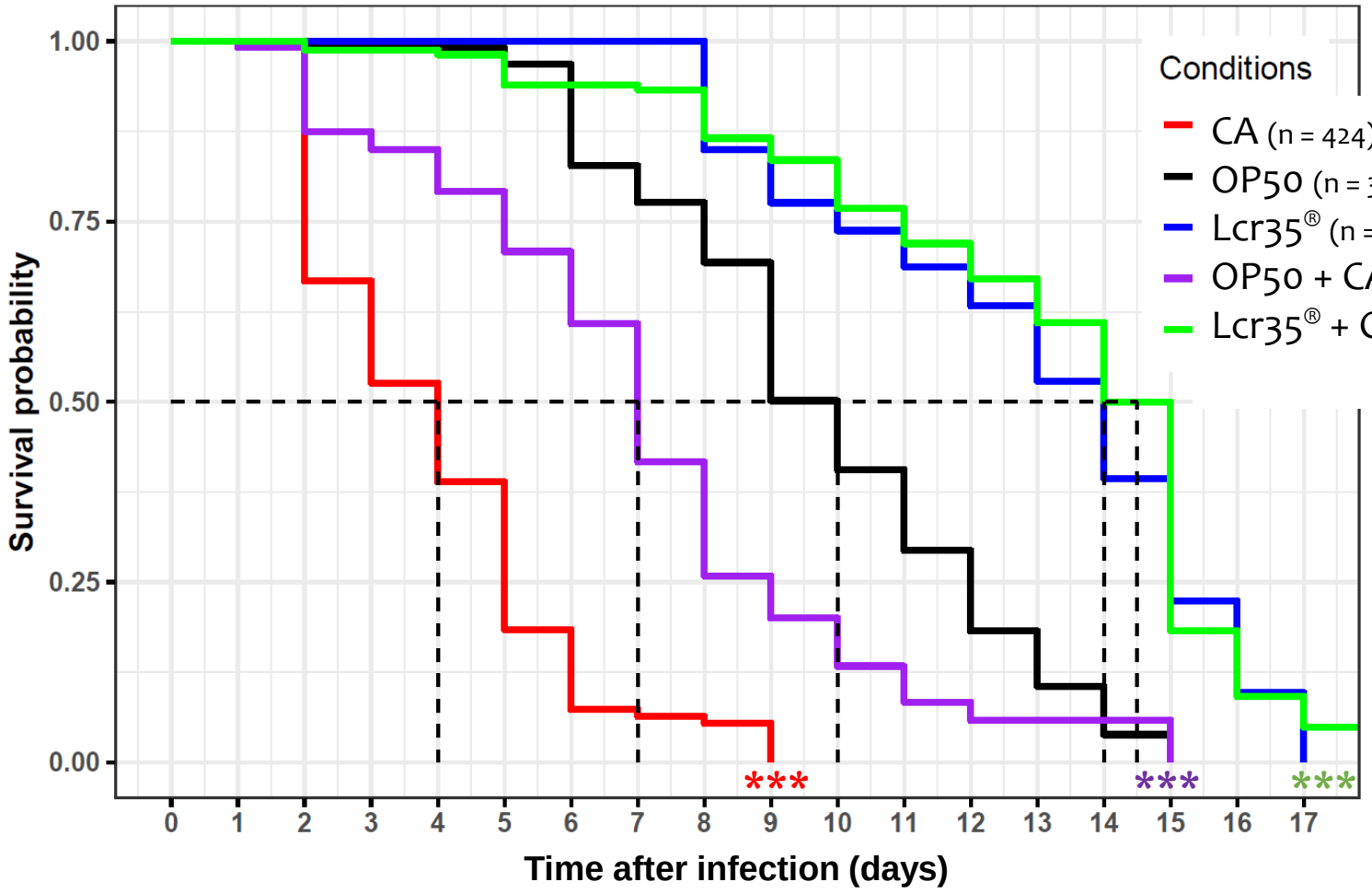
Methodology

Synchronized adult worms

- Monotypic infection
  Lcr35® or *C. albicans*
- Lcr35® preventive treatment (4 h) + *C. albicans* (2h)

→
- ☛ Survival assay
- ☛ Gut colonization
- ☛ RT-qPCR
- ☛ DAF-16 cellular localisation

C. elegans survival after Lcr35® and/or *C. albicans* infection



C. albicans pathogen – MLS = 4 days

Lcr35® +/- *C. albicans* increases MLS from 9.5 to 14 days

⇒ **Lcr35® prevents candidiasis**

MLS: mean lifespan

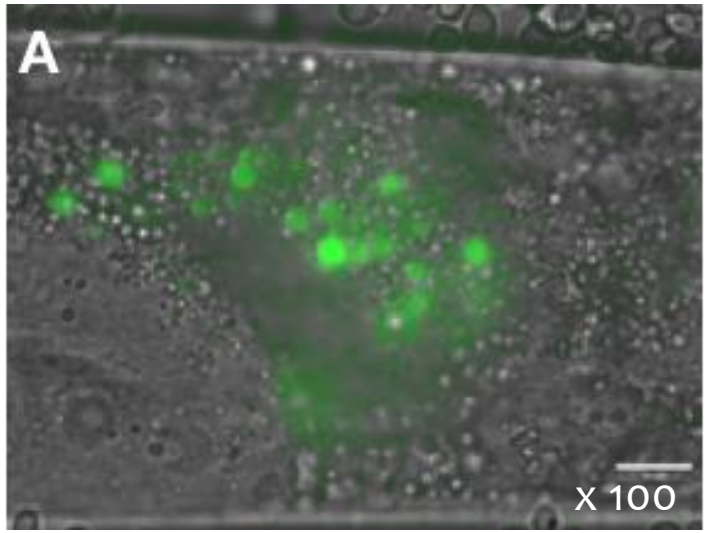
Log rank test ; *** : p < 0,001

Protocol adapted from De Barros *et al.* 2018

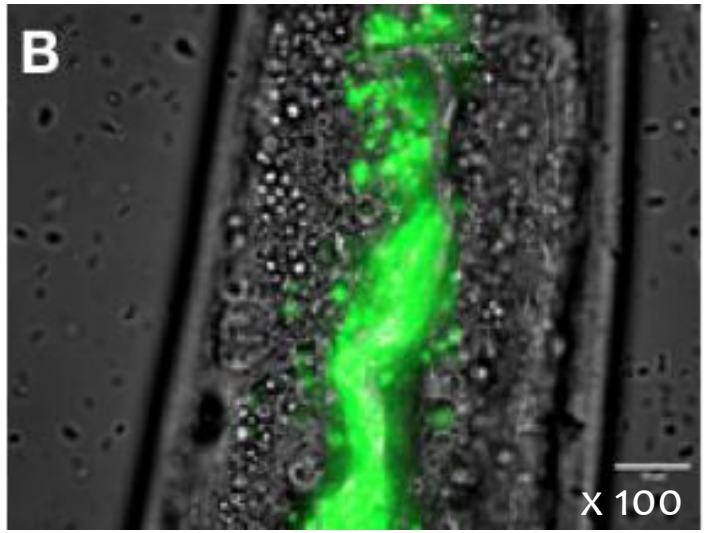
C. elegans gut colonization by *C. albicans*

C. elegans infected by *C. albicans*

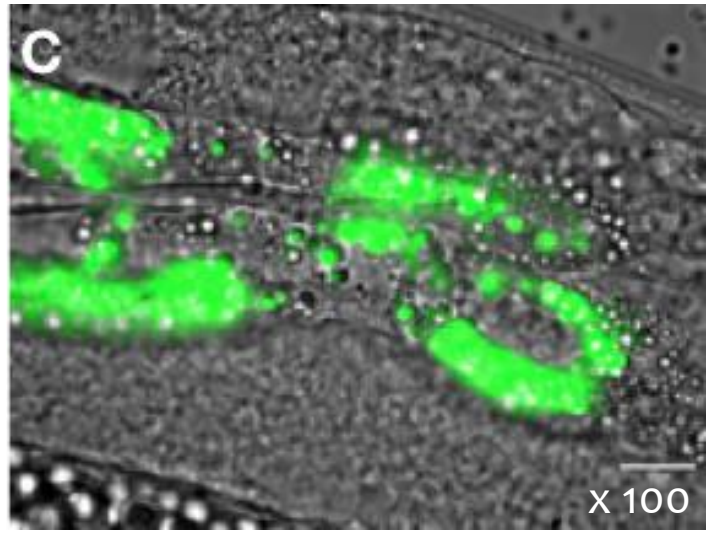
Without treatment



OP50 preventive treatment



Lcr35® preventive treatment



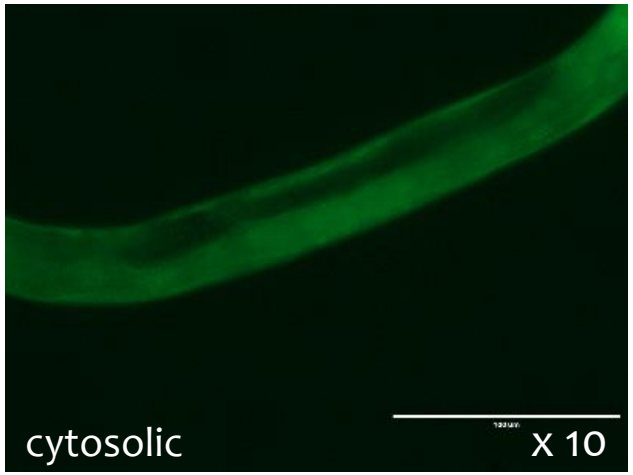
Incubation time on
Rhodamine 123 labelled-*C. albicans*: 72 hours
OP50 / Lcr35®: 4 hours

Whatever the preventive treatment (or not),
***C. albicans* is present in *C. elegans* gut**

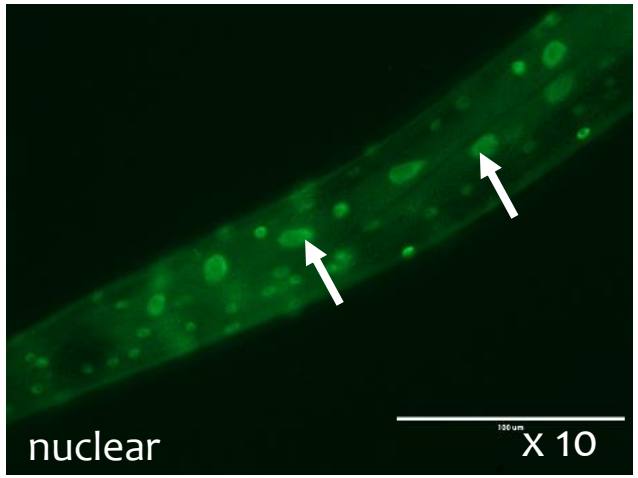
DAF-16 cellular localization

C. elegans TJ356 mutant (DAF-16::GFP) strain fed (4 hours) on:

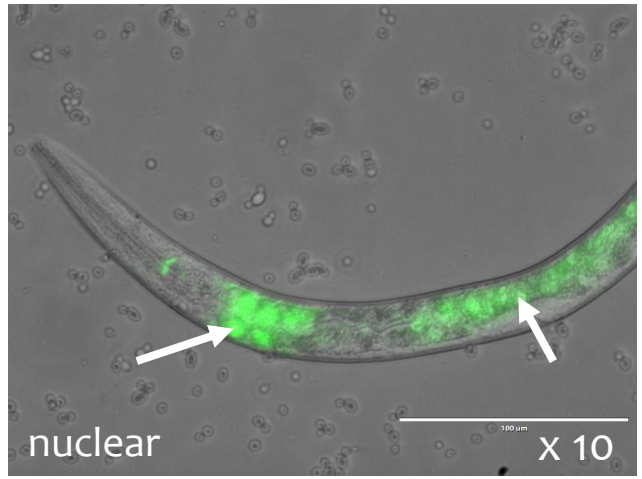
E. coli OP50



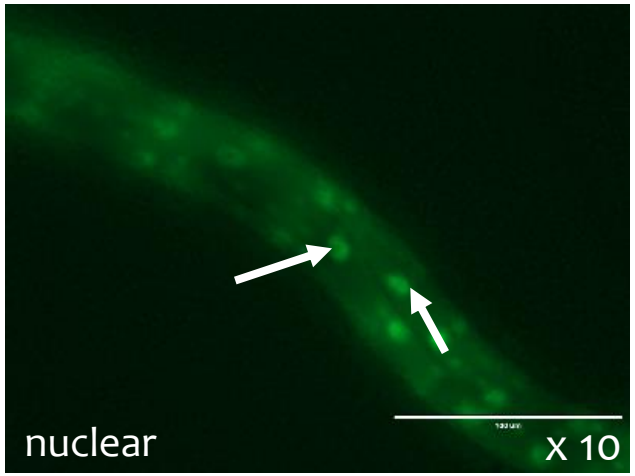
Lcr35®



Lcr35® + *C. albicans*



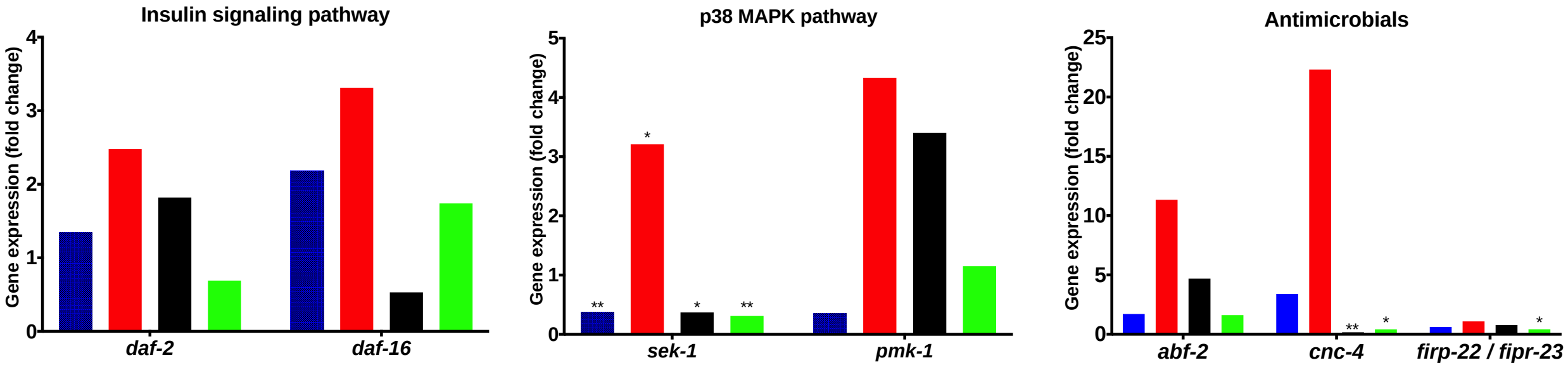
C. albicans



Both Lcr35® and *C. albicans* induce DAF-16 translocation into nuclei

Regulation of downstream genes: same or not ?

C. elegans gene expression



Lcr35® upregulates *daf-16*, downregulates p38 MAPK, *abf-2* and *fipr-22/23*
C. albicans upregulates all genes
Lcr35® preventive treatment: downregulation of *daf-2*, *sek-1* and antimicrobials

With Lcr35® as a preventive treament, *C. elegans* seems to not « detect » the pathogen

Anova test with LSD
* p < 0,05 ; ** p < 0,01 ; *** p < 0,001

Conclusion

- *C. albicans*:
  - Is pathogenic for *C. elegans* (shorten lifespan)
  - Colonizes the whole gut tract
  - Induces a strong immune response

- Lcr35®:
  - Increases *C. elegans* lifespan
  - Provides a full protection against candidiasis
  - Does not inhibit *C. albicans* colonization
  - Down regulates the immunity gene expression

Poupet *et al.*, submitted in Frontiers in Microbiology

Further investigations

- Mechanistic study of the interaction between host and Lcr35® / *C. albicans*
  - Modulation of *C. elegans* wild-type whole transcriptome (RNAseq on going)
  - Use of *C. elegans* mutants
  - Modulation of yeast virulence genes by Lcr35®
- Study of antipathogens properties of a formulated Lcr35® strain
- Development of new LBPs based on Lcr35® (marketing authorization)

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- biose®

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- Dr. Taous Saraoui (UCA)

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biose®

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Thank you for your attention

Any questions?