Probio-M9, a breast milk-originated probiotic, alleviates mastitis and enhances antibiotic efficacy: Insights into the gut-mammary axis.

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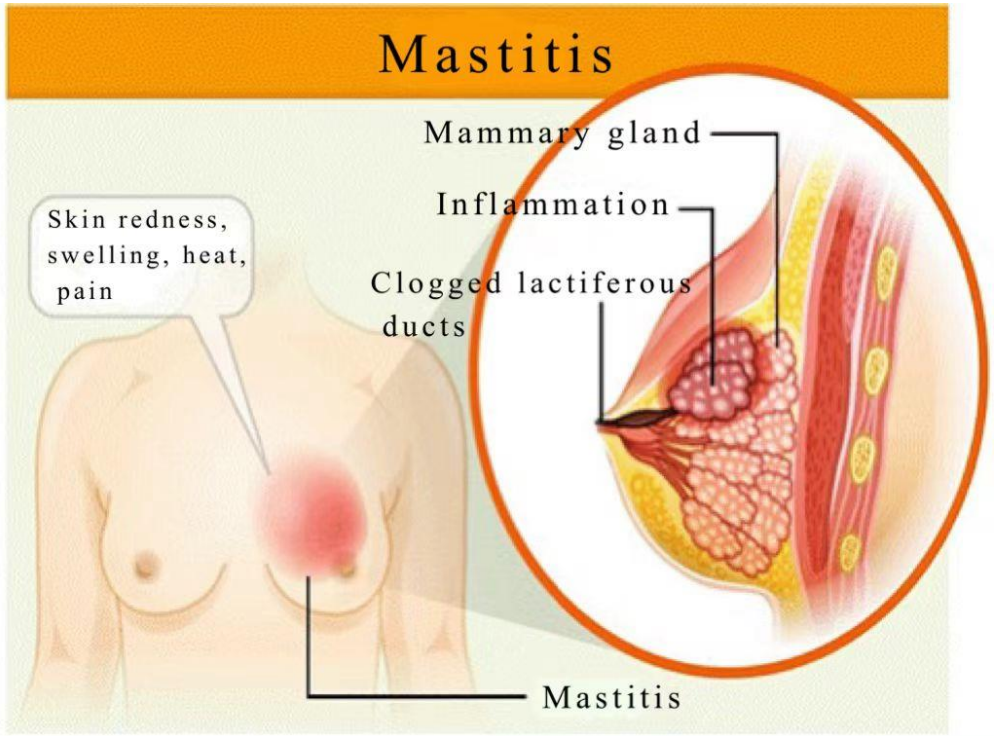
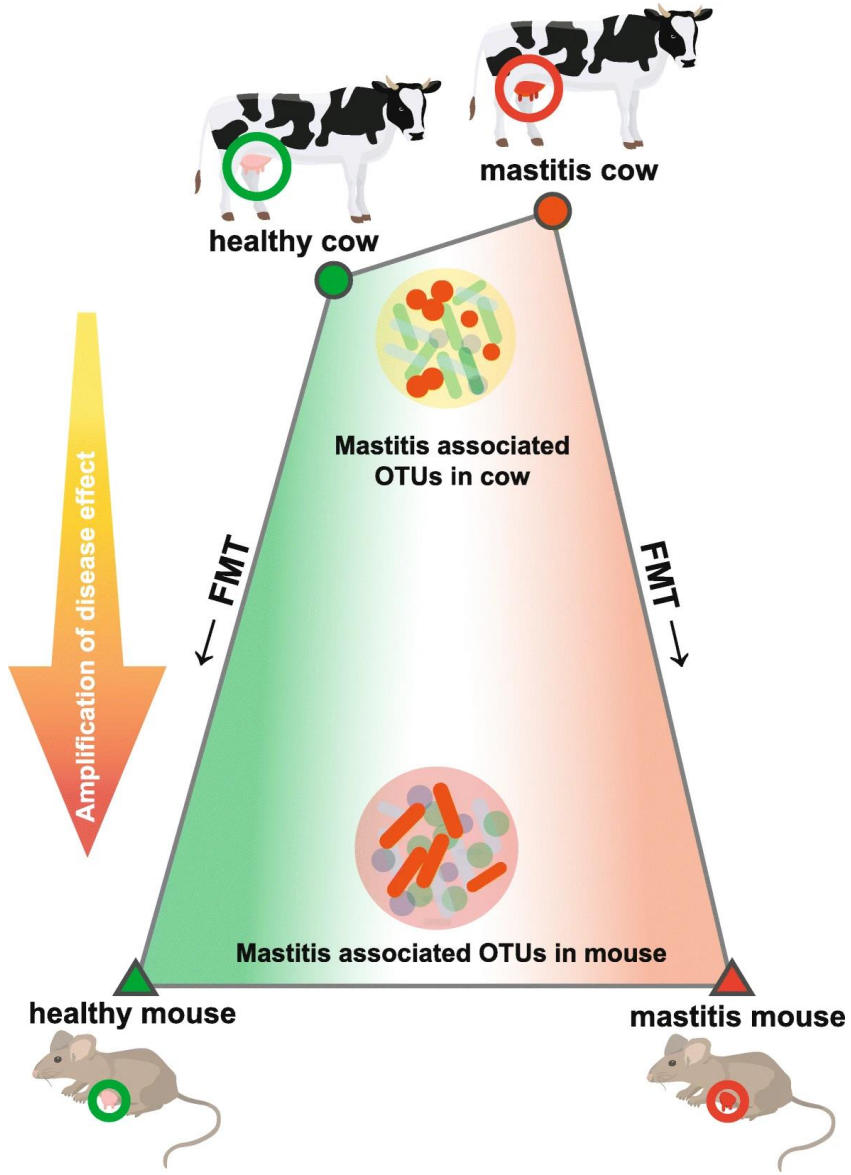
Jie Yu#, Weicheng Li#, Ruibo Xu#, Xiaoye Liu#, Guangqi Gao, Lai-Yu Kwok, Yongfu Chen, Zhihong Sun, Wenjun Liu, Heping Zhang*. Probio-M9, a breast milk-originated probiotic, alleviates mastitis and enhances antibiotic efficacy: Insights into the gut-mammary axis. . ***iMeta*** 3: e224. https://doi.org/10.1002/imt2.224

Background

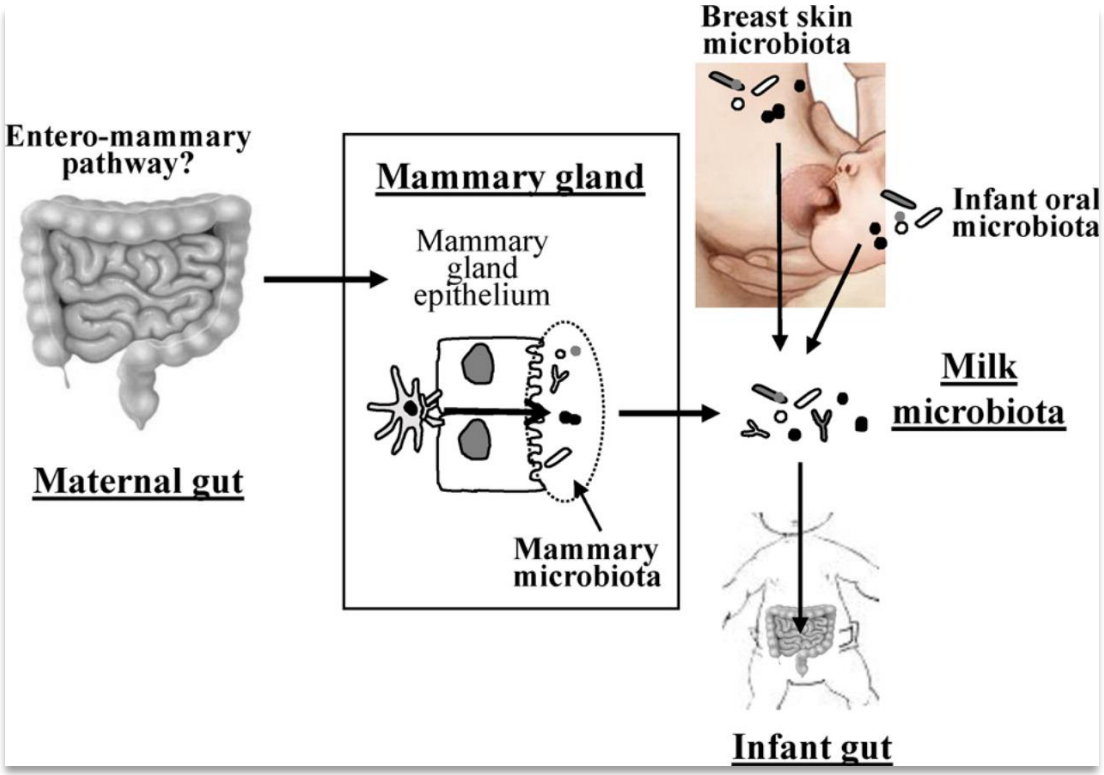


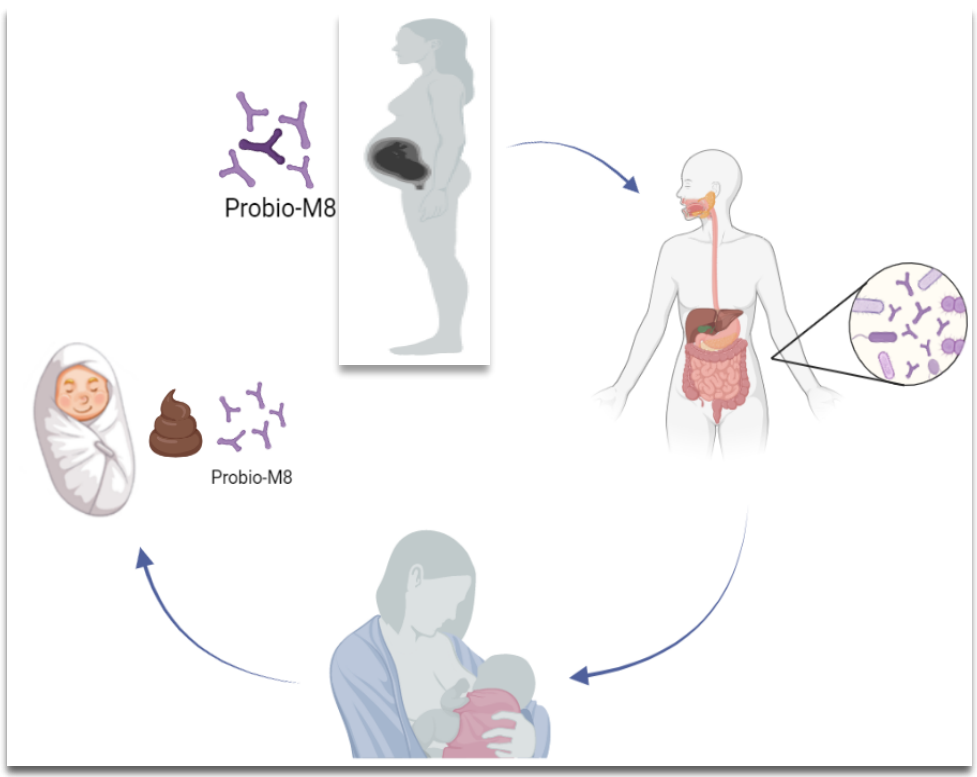


- Mastitis, a prevalent condition that affects nearly all lactating mammals. Mastitis leads to substantial economic losses worldwide due to the significant reduction in milk quality and quantity, directly impacting profitability and productivity.
- Probiotics may be an effective and safe strategy to treat mastitis.

Ma, C., Sun, Z., Zeng, B. et al. Cow-to-mouse fecal transplantations suggest intestinal microbiome as one cause of mastitis. Microbiome 6, 200 (2018). https://doi.org/10.1186/s40168-018-0578-1

Background



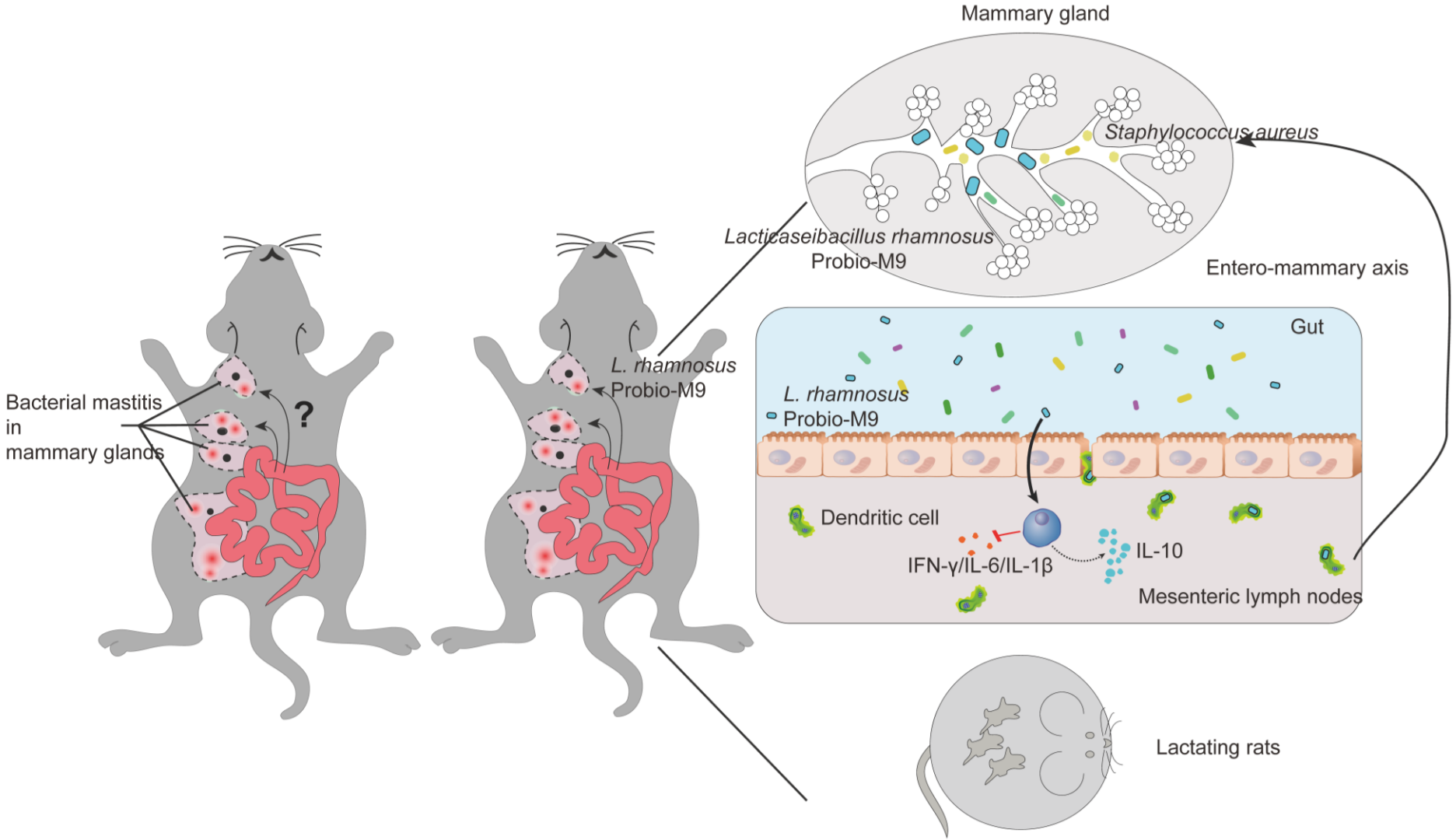


- Gut microbes can be transferred from mother to infant.

Fernández L, Langa S, Martín V, et al. The human milk microbiota: origin and potential roles in health and disease. Pharmacol Res. 2013;69(1):1-10. doi:10.1016/j.phrs.2012.09.001

Zhong Z, Tang H, Shen T, et al. Bifidobacterium animalis subsp. lactis Probio-M8 undergoes host adaptive evolution by glcU mutation and translocates to the infant's gut via oral-/entero-mammary routes through lactation. Microbiome. 2022;10(1):197. doi:10.1186/s40168-022-01398-6

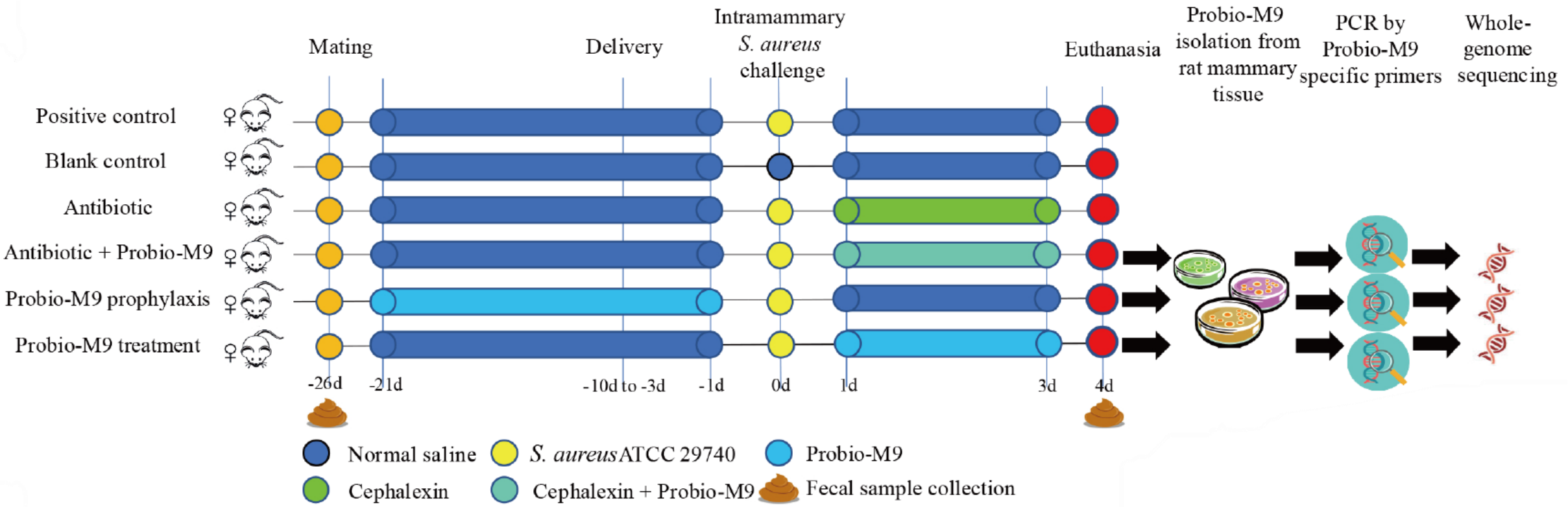
Highlights



- In this study, we evaluated the efficacy of the probiotic strain, *Lacticaseibacillus rhamnosus* Probio-M9, in treating mastitis by using a rat mammary model infected with *Staphylococcus aureus*. And the existence of a pathway of the gut-mammary translocation of Probio-M9.

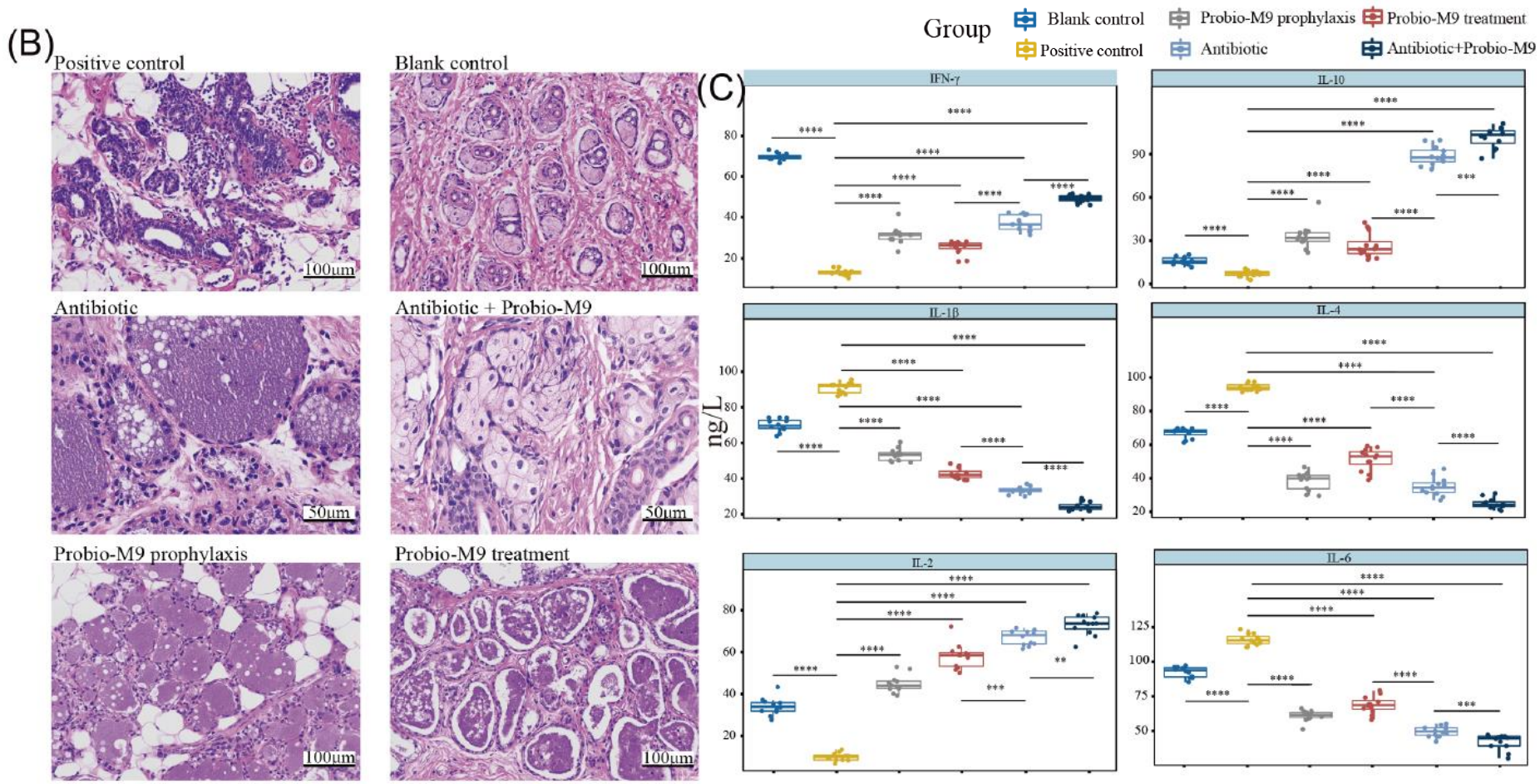
Experimental Design I

Experiment I



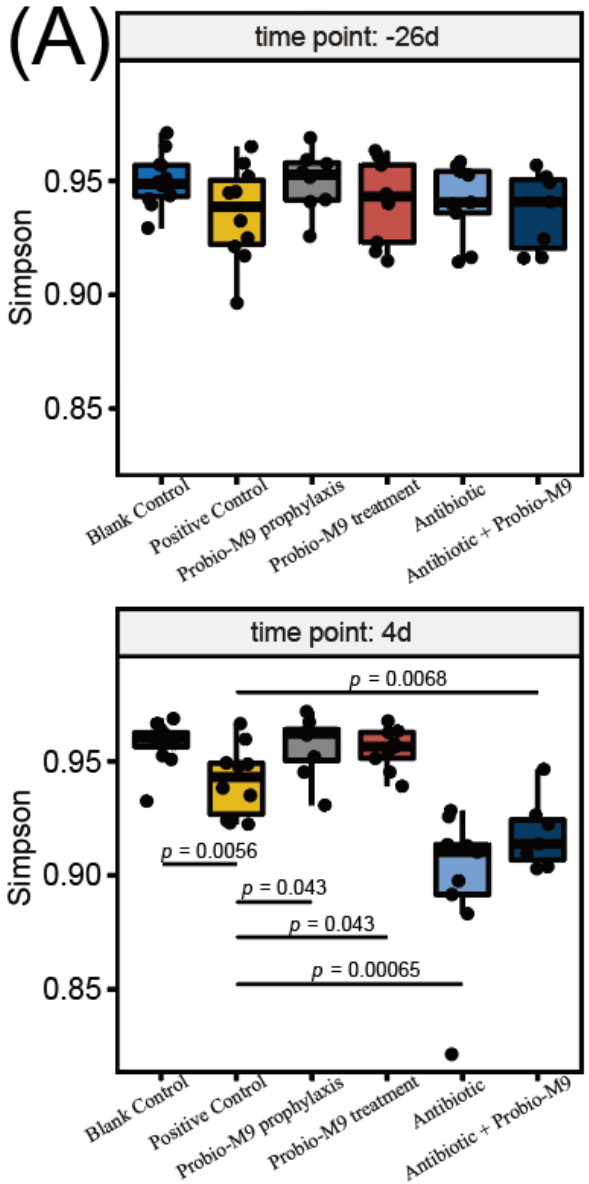
- In experiment I, 72 female rats were randomly divided into six groups: positive control, blank control, antibiotic, antibiotic + Probio-M9, Probio-M9 treatment, and Probio-M9 prophylaxis.
- After delivery, all groups, except for the blank control group, underwent *S. aureus* infection via intra-mammary injection on day 0. Fecal samples were collected at two time points: day -26 and day 4. And the mammary glands of rats that were fed Probio-M9 were collected at day 4.

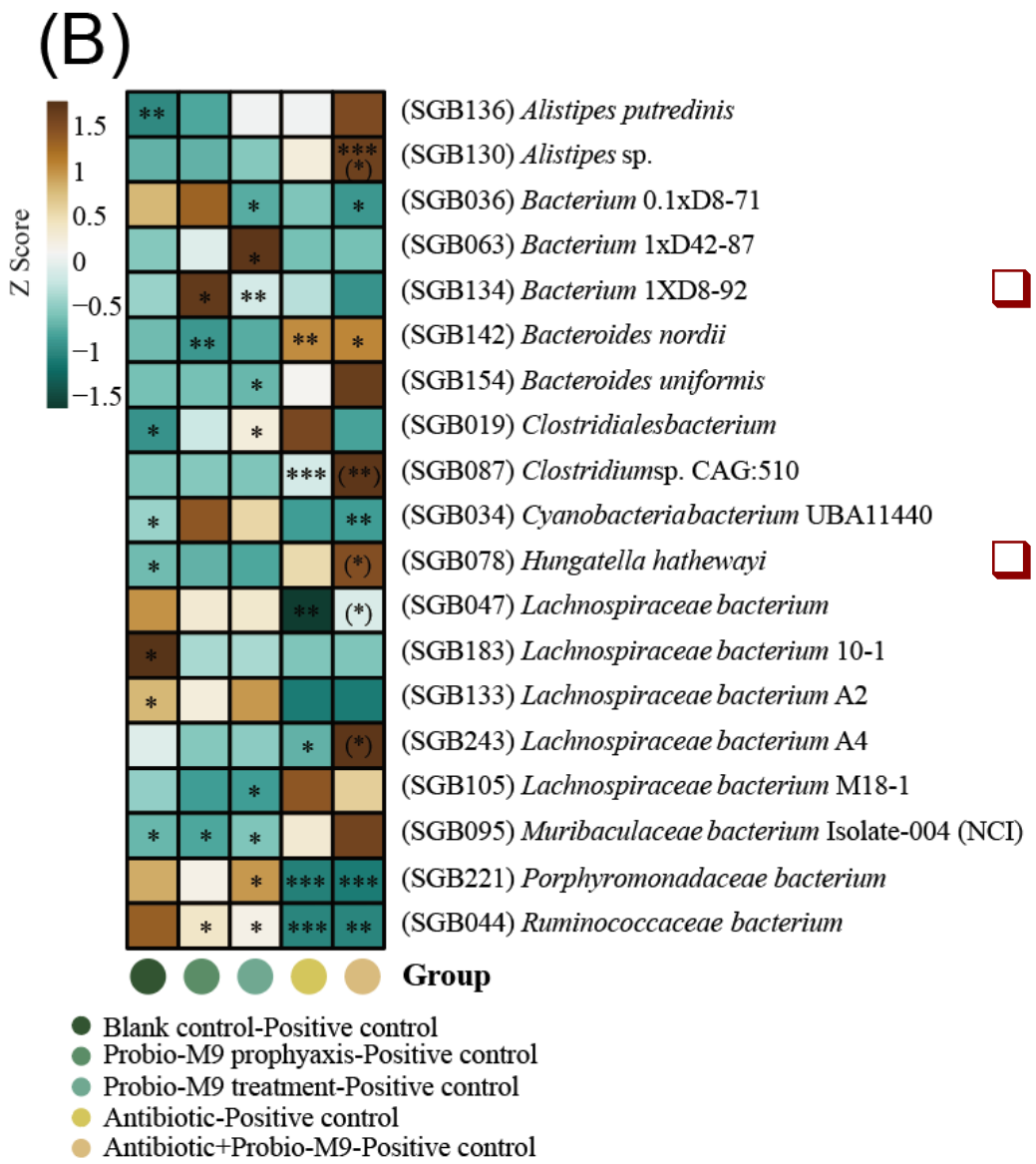
Results of Experiment I



- The Probio-M9 prophylactic group and the Probio-M9 treatment group showed little lymphocyte infiltration in the acinar cavity and stroma.
- Probio-M9 inhibits inflammation, Th1/Th2 balance returned to normal levels.
- Probio-M9 relieves mastitis and enhances antibiotic efficacy.

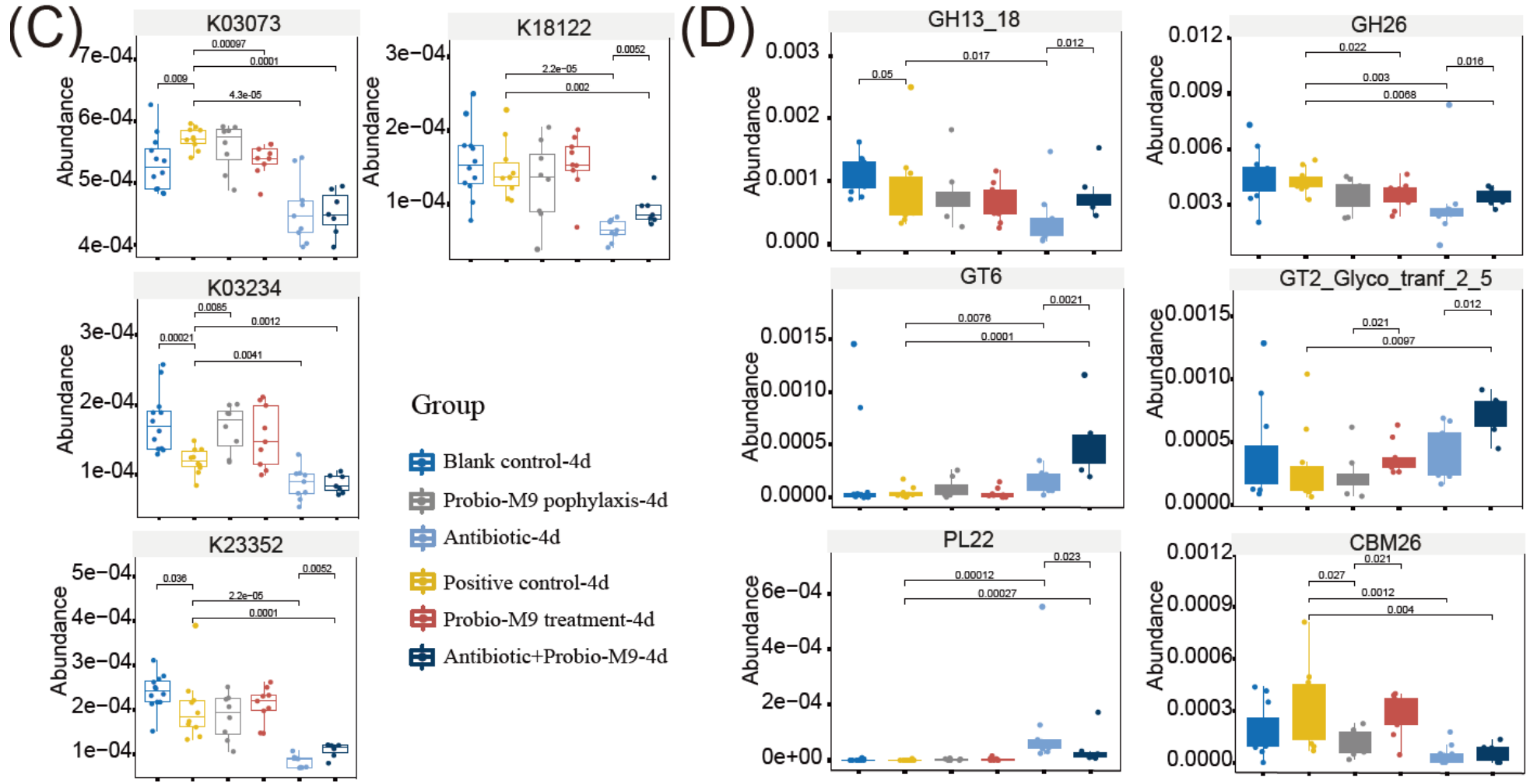
Results of Experiment I





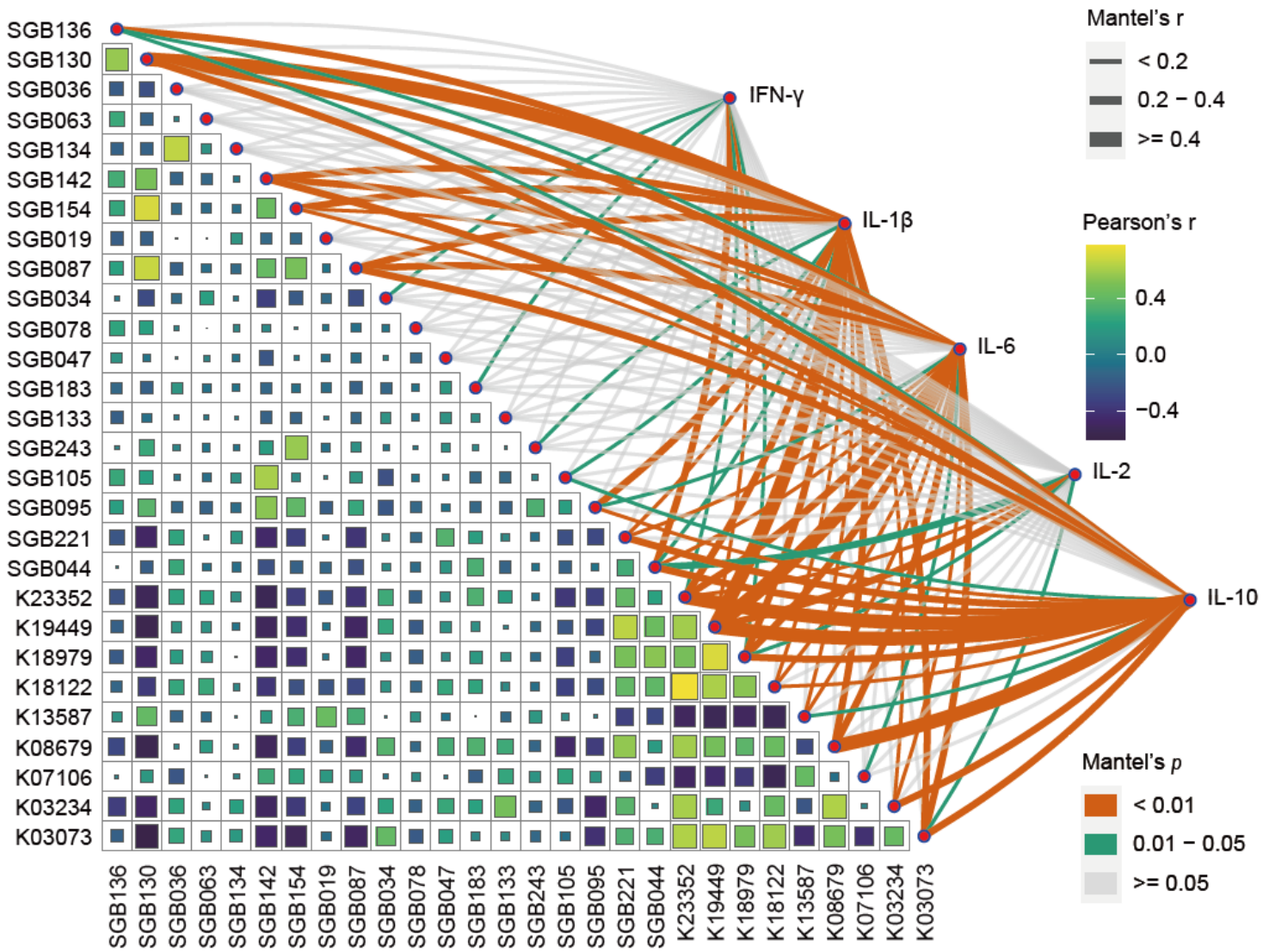
- Probio-M9 effectively relieved the lower alpha diversity caused by mastitis.
- Probio-M9 increased the abundance of *Alistipes* sp. and decreased the abundance of *Bacteroides nordii* significantly.

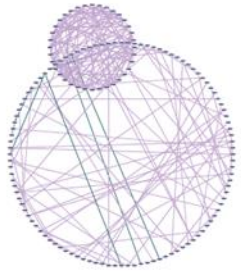
Results of Experiment I



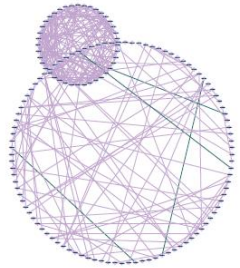
- Administration of Probio-M9 significantly alleviated the alterations in the gene abundance of specific KEGG and CAZy.

Results of Experiment I

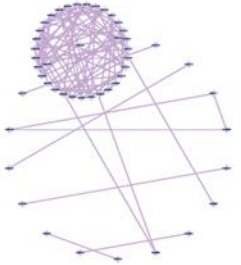




Probio-M9 treatment at 4d



Probio-M9 prophylaxis at 4d

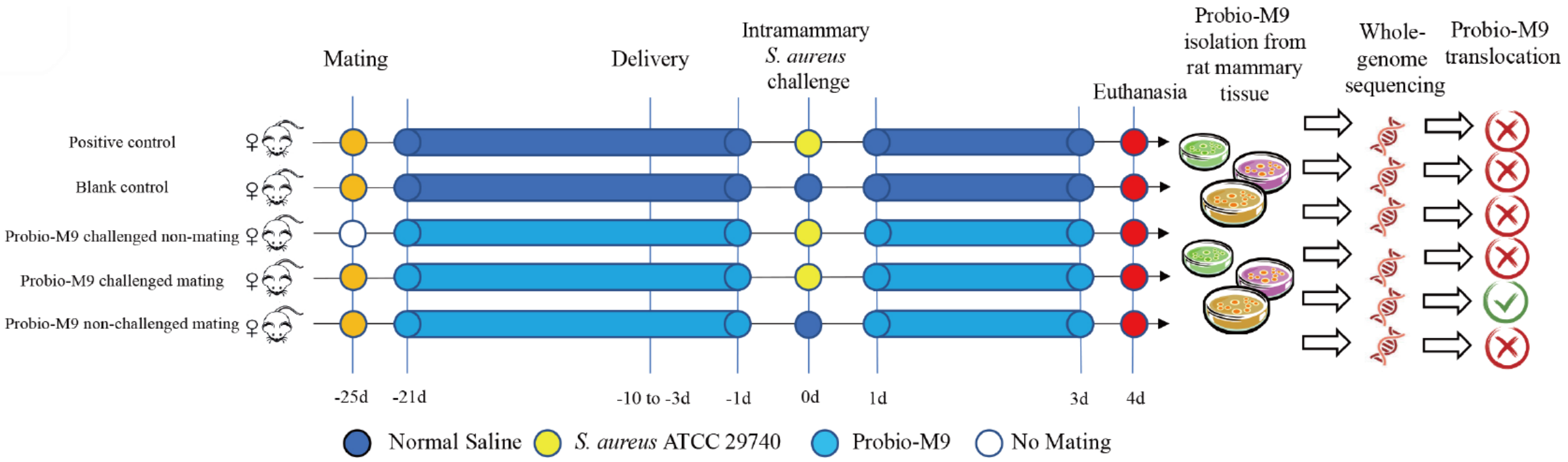


Antibiotic + Probio-M9 at 4d

- Probio-M9 enhanced the interactions between microbiota and metabolic genes.
- All five cytokines (IFN-γ, IL-1β, IL-6, IL-2, and IL-10) showed positively correlations with K19449, K23352, and *Ruminococcaceae bacterium* (p<0.05，R>0.2).
- Aforementioned species and metabolic pathways may play a key role in modulating immunity.

Experimental design II and results

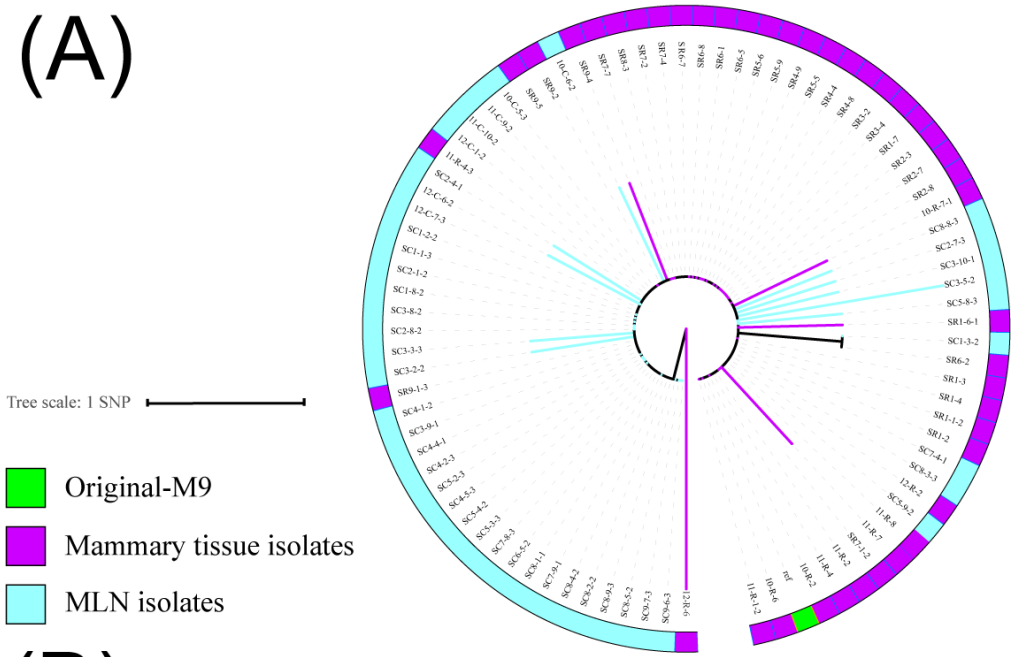
Experiment II



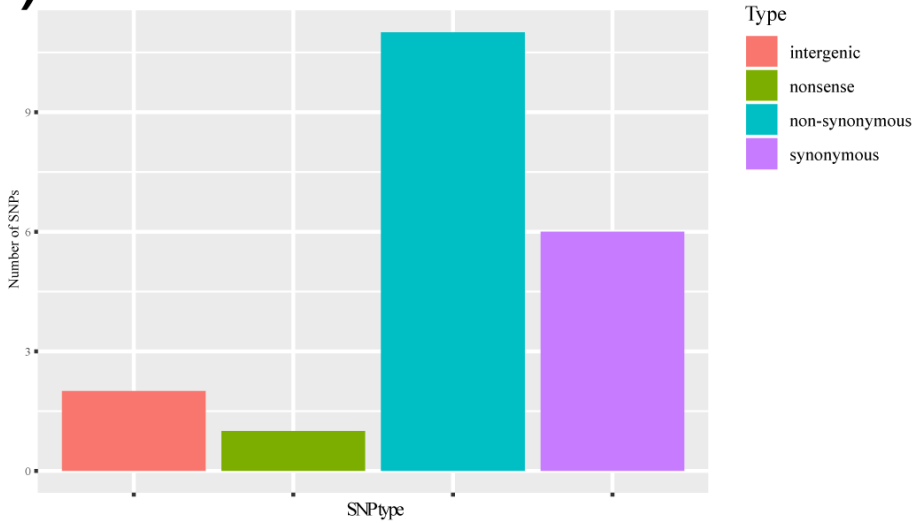
- We conducted Experiment II, which closely resembled Experiment I but with two key modifications. Firstly, we excluded antibiotic treatment from the experimental design. Secondly, we included two additional groups: a non-mated (non-lactating) group and a group of rats not challenged with *S. aureus* but administered Probio-M9.
- Both *S. aureus*-induced mastitis and lactation were necessary prerequisites for bacterial translocation to occur, and bacterial translocation likely occurred through the lymphatic system.

Results of Experiment II

(A)



(B)



- 85 cultures were isolated exclusively from and MLN of lactating rats.
- There were only 20 SNPs across all isolates and no common mutations were found between the original Probio-M9 strain and the 85 cultures.
- These results indicate a high level of relatedness between these 85 isolates (collected from mammary gland and MLN of the 12 rats) and Probio-M9.

Summary

- Probio-M9 has the potential to alleviate mastitis and mitigate the adverse effects of antibiotic therapy.
- Through genomic-level analysis, we have identified instances of independent Probio-M9 translocation from the rat gut to the mammary gland, potentially involving the lymphatic system.
- Moreover, we have confirmed the requirement of lactation and the development of bacterial mastitis for bacterial translocation. While the precise mechanism of probiotic translocation remains unclear, our results suggest a selective rather than random process.

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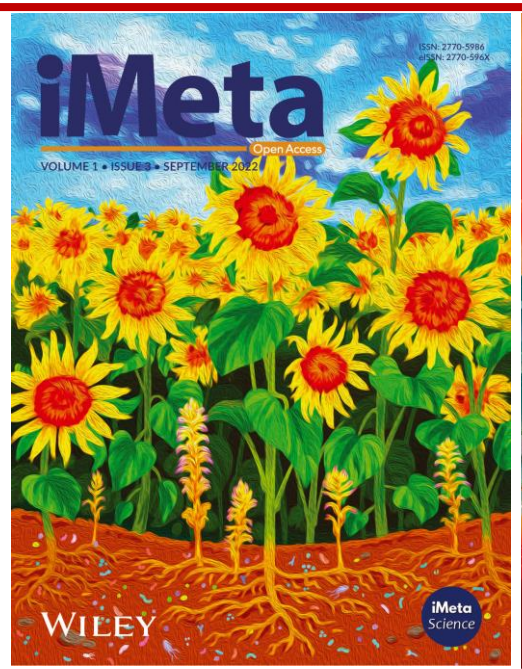

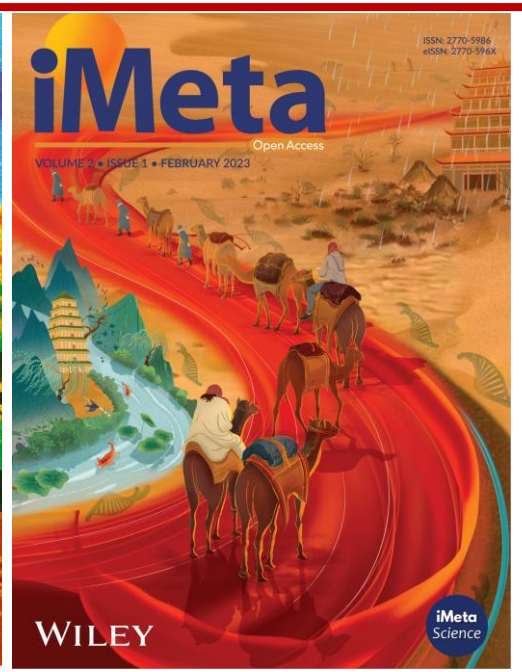

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