In vivo modeling of dermatophytosis reveals infection dynamics influenced by the ecological niche of the fungus but a conserved host immune response

R. Vanberg[1], F. Maréchal[1], J. Piret[2], W. Poirier[1*] and B. Mignon[1*]

1. *Department of Infectious and Parasitic Diseases, Laboratory of Mycology, FARAH, Faculty of veterinary Medicine, University of Liege, Belgium*
2. *Department of Morphology and Pathology, Laboratory of Histology, FARAH, Faculty of veterinary Medicine, University of Liege, Belgium*
**These co-authors contributed equally to this work*

Introduction

Dermatophytoses, commonly known as "ringworm" or "*tinea*," are superficial infections caused by keratinophilic filamentous fungi called dermatophytes, which affect both humans and animals (Weitzman and Summerbell, 1995). Dermatophytes are classified according to their natural reservoir into **three ecological groups** which influence their transmission, host specificity, and pathogenicity (de Hoog *et al.,* 2017).

- **anthropophilic** species are primarily adapted to humans
- **zoophilic** species infect animals and are most often zoonotic
- **geophilic** species are typically soil saprophytes, generally non-pathogenic except for a few facultative parasitic species

Aim of the study

The aim of this study was to compare infection mechanisms among dermatophyte species from the three ecological niches using an *in vivo* murine infection model.

Material and Methods

To characterize the infection mechanisms, we employed our murine infection model using three dermatophyte species obteined from the collection of the Institut of Hygiene and Epidemiology – Mycology (IHEM) : ***Trichophyton rubrum*** (anthropophilic), ***Microsporum canis*** (zoophilic), and ***Nannizzia gypsea*** (geophilic). **Clinical follow-up**, performed daily for 22 days. **Histopathological analyses** were conducted to evaluate infection severity and tissue damages on days 1, 3 and 5 post-infection (PI). Additionally, the **relative mRNA expression levels of host cytokines** (*IL-1ß*, *IL-17A*, and *IL-22*) **and fungal proteases** considered as potential virulence factors (*deuterolysin*, *subtilisin 6*, and *subtilisin 10* were quantified on days 1 to 5 PI to characterize the host–pathogen interaction.

Clinical follow-up

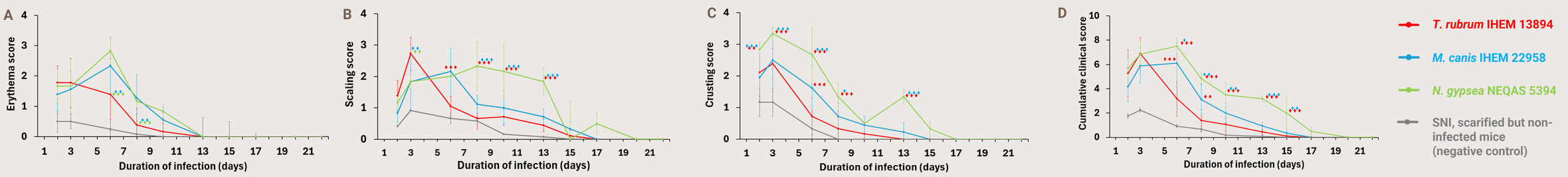

Figure 1: Development of the infection by *T. rubrum* IHEM 13894, *M. canis* IHEM 22958 and *N. gypsea* NEQAS 5394 in mice. The lesions that developed in the infected mice were monitored until complete recovery, with clinical emphasis on the intensity of (A) erythema, (B) scaling and (C) crusting. (D) A cumulative clinical score was calculated based on these three clinical signs. ♦ $P < 0.05$; ♦♦ $P < 0.01$; ♦♦♦ $P < 0.001$ (n=9)

Host immune response

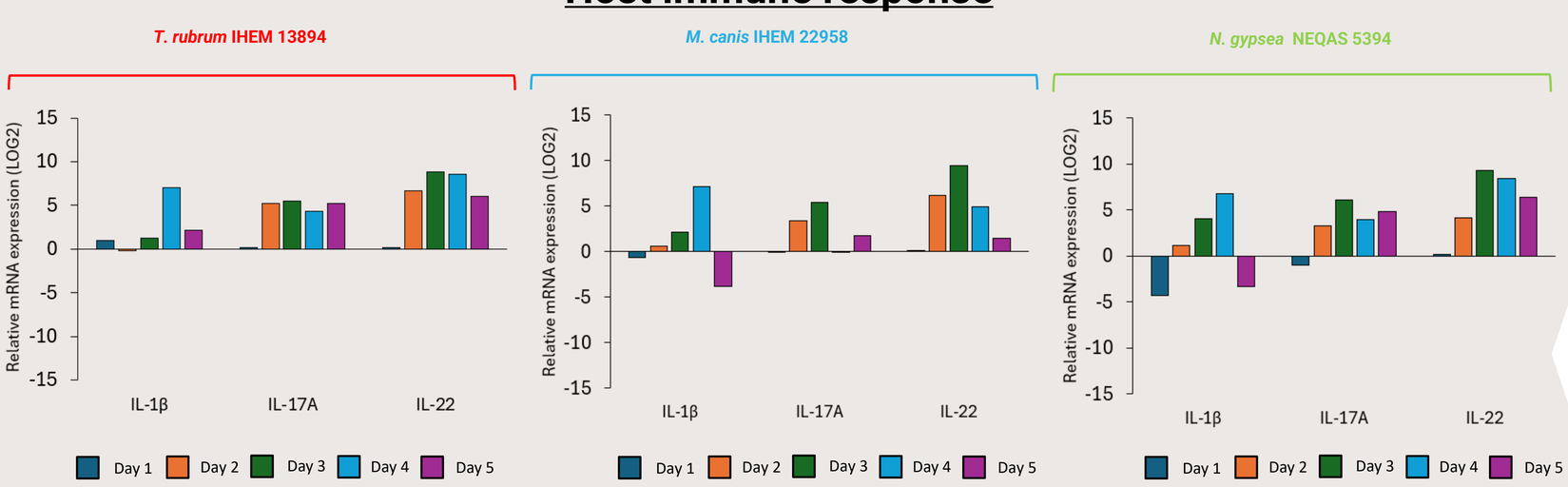

Figure 3: Expression of host pro-inflammatory cytokines during infections of mice with *T. rubrum IHEM 13894*, *M. canis IHEM 22958*, and *N. gypsea NEQAS 5394*. The relative mRNA expression of murine pro-inflammatory cytokines was assessed by RT-qPCR after total RNA extraction from skin biopsies on day 1 to 5 PI. The mRNA expression was normalized using the level of the same transcript measured under control conditions (scarified but non-infected [SNI] mice). *IL*, *interleukin* (n=1)

Fungal gene expression

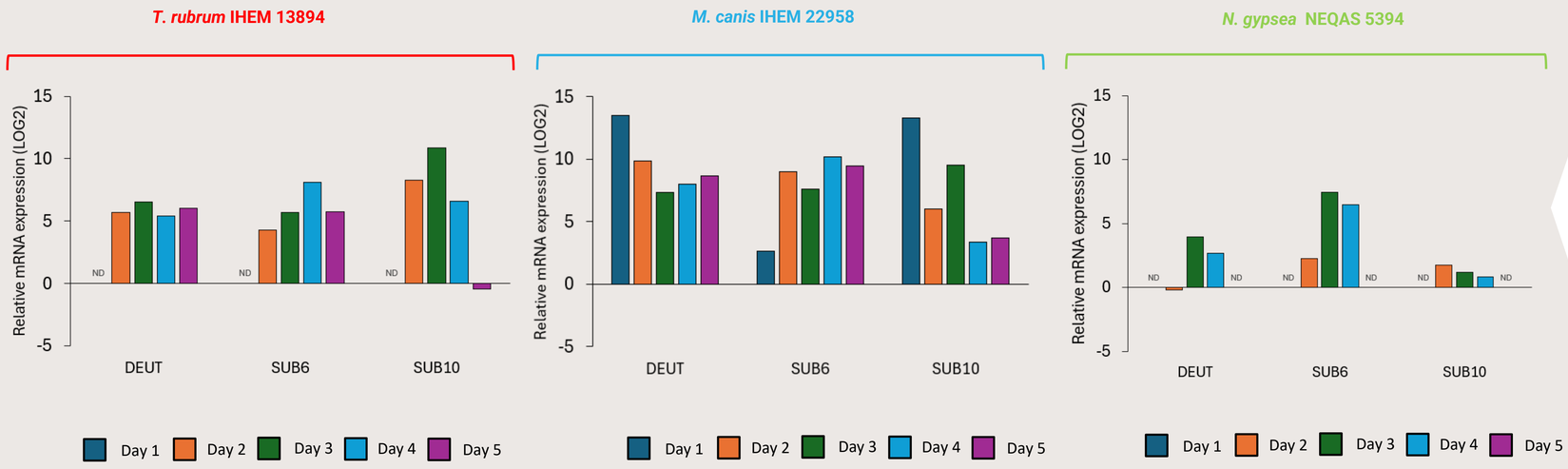

Figure 4: Expression of fungal proteases during infections of mice with *T. rubrum IHEM 13894*, *M. canis IHEM 22958*, and *N. gypsea NEQAS 5394*. . The relative mRNA expression of fungal proteases was assessed by RT-qPCR after total RNA extraction from skin biopsies on day 1 to 5 PI. The mRNA expression was normalized using the level of the same transcript measured under control conditions (*in vitro* cultured mycelium). ND, not-done; *DEUT*, *deuterolysin* ; *SUB*, *subtilisin* (n=1)

Histopathology

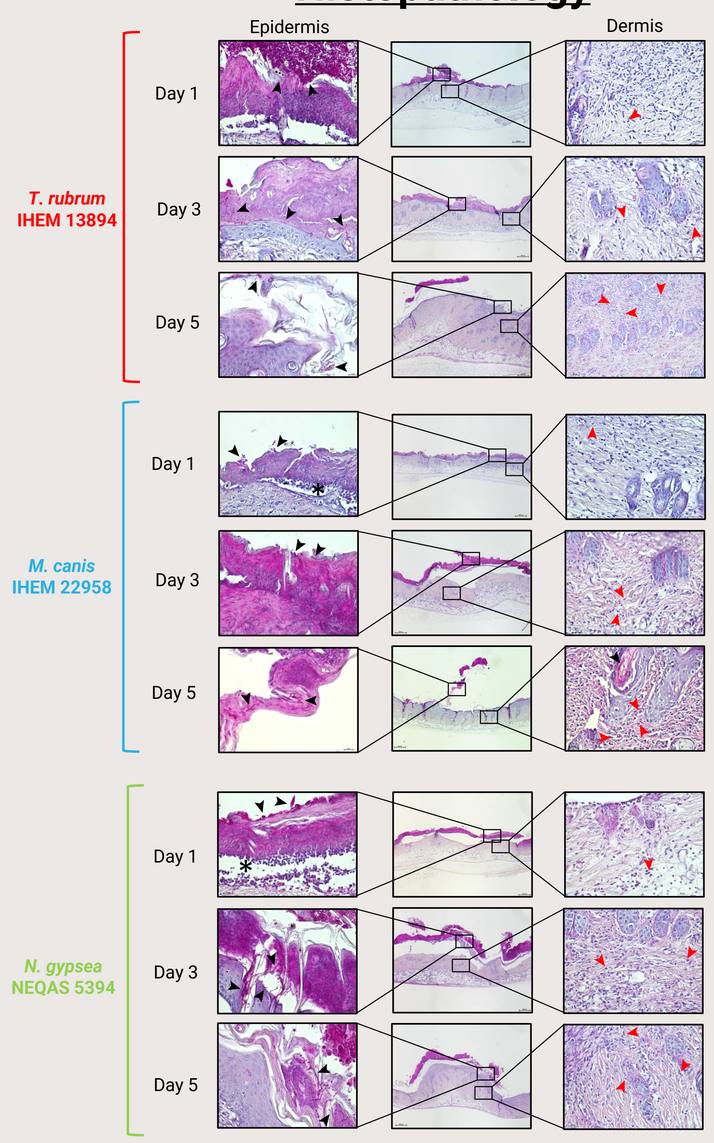

Figure 2: Fungal invasion and inflammatory cell infiltration during *T. rubrum* IHEM 13894, *M. canis* IHEM 22958 and *N. gypsea* NEQAS 5394 infections in mice. Biopsies were recovered on day 1, 3 and 5 PI, then processed for histology and periodic acid-Schiff staining with hematoxylin counterstaining. The presence of epithelial pustules within the infected tissue is indicated by asterisks, fungi by black arrows (➤) and neutrophils by red arrows (➤).

Results overview

- As shown in the clinical follow-up and histopathological analyses, **infection dynamics** varied between species:
  - ***Trichophyton rubrum*** (anthropophilic) caused **moderate lesions**
  - ***Microsporum canis*** (zoophilic) caused a more persistent infection with **delayed healing**
  - ***Nannizzia gypsea*** (geophilic) caused **acute and severe inflammation**
- **Host cytokine responses** were dominated by a **Th17-driven pathway**, a T CD4+ differentiation route in which the three interleukins studied (IL-1β, IL-17A and IL-22) play key roles.
- All fungi species **overexpressed** the three **fungal proteases** studied during infections in mice.

Conclusion

Overall, our results highlight a **unique infection profile** shaped by clinical progression, tissue invasion, host cytokine activity, and modulation of the fungal enzymatic arsenal, each **influenced by the dermatophytes' ecological niche**. This work may pave the way for future investigations aimed at elucidating the molecular mechanisms driving **niche-specific pathogenicity**, **refining host–pathogen interactions** and identifying potential immunomodulatory or antifungal targets to **improve therapeutic strategies**.

References

- de Hoog, G.S. *et al.*, 2017. Mycopathologia. doi:10.1007/s11046-016-0073-9
- Faway, E. *et al.*, 2021. J Fungi. doi:10.3390/jof7121029
- Faway, E. *et al.*, 2025. J Invest Dermatol. doi:10.1016/j.jid.2024.08.010
- Weitzman *et al.,* 1995. Clinical Microbiology Reviews. doi:10.1128/cmr.8.2.240