# *Leishmania infantum* dampens neurotoxic NO release by infected macrophages in the presence of amyloid β

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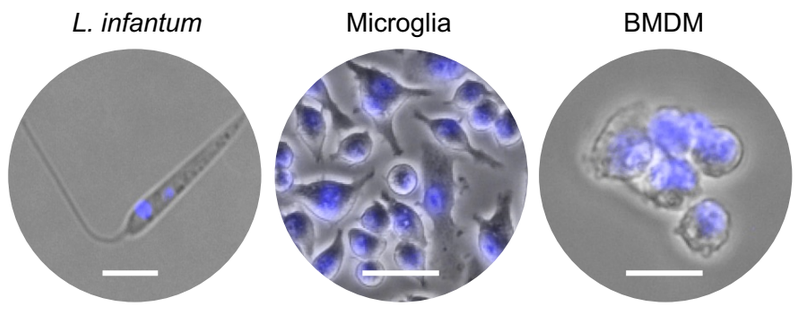
## INTRODUCTION

The innate immune response and chronic neuroinflammation are at the forefront of Alzheimer's disease (AD) pathology, the most frequent cause of dementia worldwide[1]. Amyloid β (Aβ) deposition in the brain activates microglia (the macrophages of the CNS), which in turn release pro-inflammatory cytokines and free radicals, including nitric oxide (NO) which is toxic to neurons, exacerbating the neuroinflammatory response[2]. Thus, interventions that downregulate the release of neurotoxic NO could be beneficial in AD. *Leishmania infantum* parasites have evolved sophisticated mechanisms to subvert macrophage functions and innate inflammatory responses, including the release of microbicidal molecules such as deadly NO[3].

## OBJECTIVE

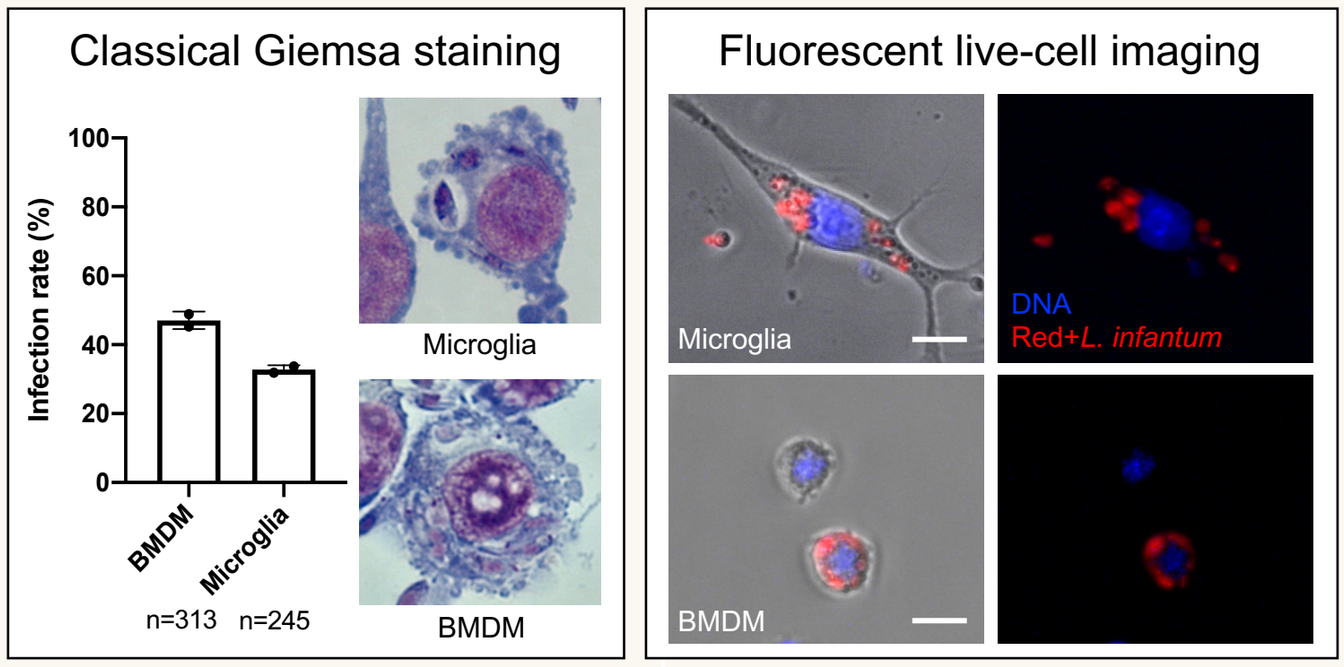
**The aim of the present study is to investigate whether *L. infantum* parasites can disrupt the innate immune functions of host macrophages, in particular the production of NO, even in the presence of Aβ.**




## RESULTS & DISCUSSION

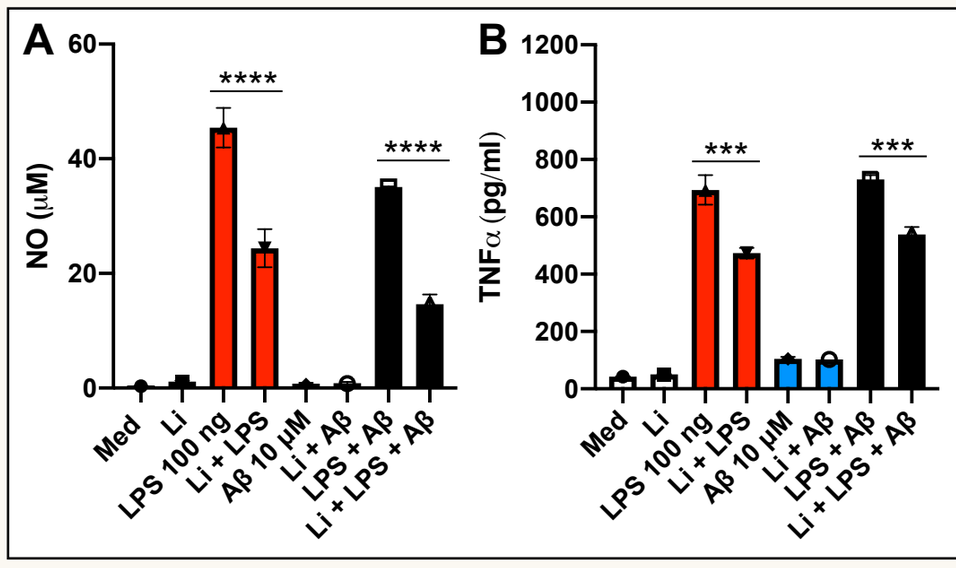
Microglia and invading bone marrow-derived macrophages (BMDM) are central to the initiation and progression of AD[1].

### 1) *L. infantum* infects both murine microglia and BMDM



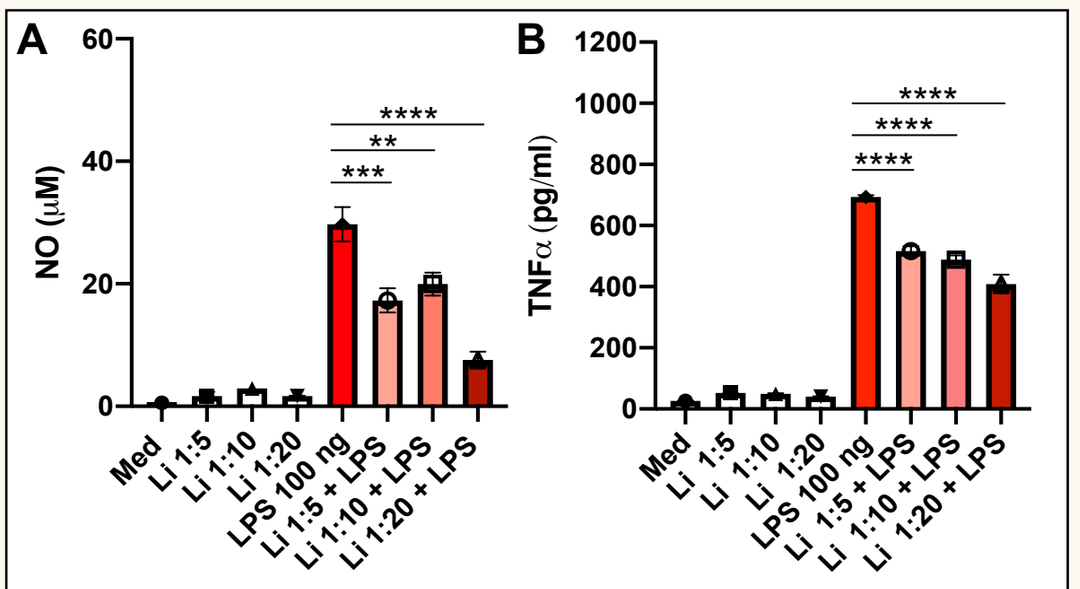

We then studied the release of nitric oxide and TNFα from microglia and BMDM, as these are two important mediators of Aβ-induced neurotoxicity and inflammation[4].

### 2) The production of neurotoxic NO and TNFα by microglia in the presence of pro-inflammatory stimuli, including Aβ, is significantly impaired by *L. infantum*



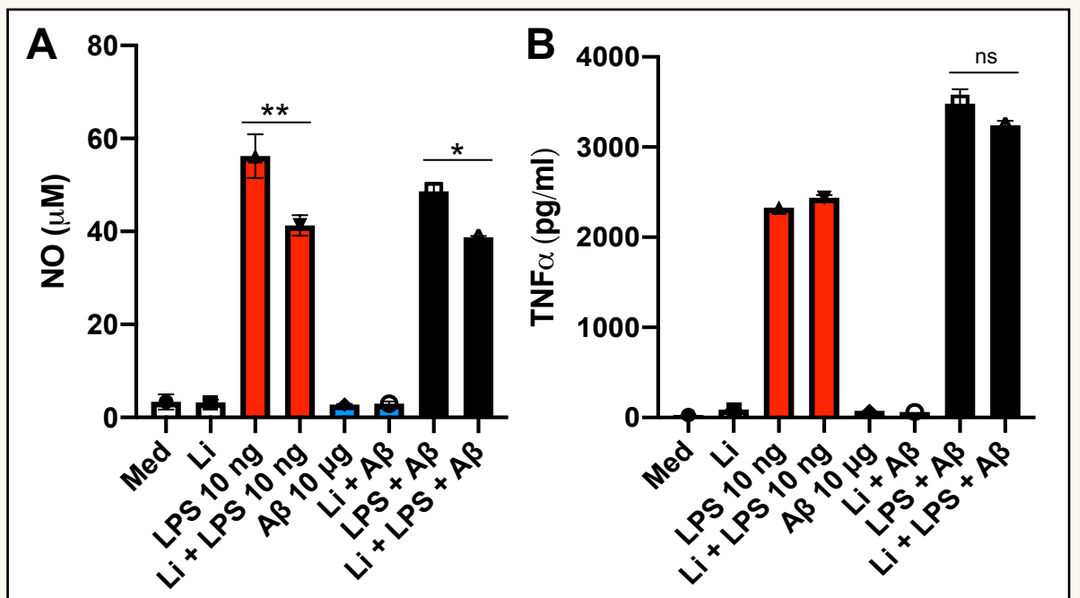

Microglia were infected with *L. infantum* (1:10 ratio cell:parasites) for 24 h in the presence of pro-inflammatory agents. Cell culture supernatants were assayed for NO by the Griess reaction (A) and TNFα (B) by ELISA. One-way ANOVA showing statistical differences (***p<0.001, ****p<0.0001).

### 3) *L. infantum*-dependent NO and TNFα reduction in LPS-treated microglia




Microglia were infected with increasing amounts of *L. infantum* parasites (1:5, 1:10 and 1:20 ratio cell:parasites) for 24 h in the presence of pro-inflammatory LPS. Cell culture supernatants were assayed for NO (A) by the Griess reaction and TNFα (B) by ELISA. One-way ANOVA showing statistical differences (**p<0.01, ***p<0.001, ****p<0.0001).

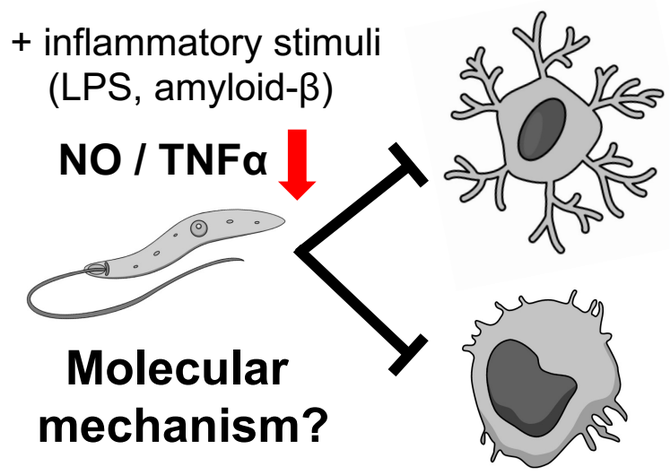
### 4) *L. infantum* dampens NO production by BMDM in LPS- and Aβ-treated macrophages, but does not alter TNFα release




BMDM were infected with *L. infantum* parasites (1:10 ratio cell:parasites) for 24 h in the presence of pro-inflammatory LPS and amyloid-β peptide. Cell culture supernatants were used to assay the NO production (A) by macrophages through the Griess reaction and TNFα (B) by ELISA test. One-way ANOVA showing statistical differences (*p<0.05, **p<0.01).

## CONCLUSIONS

These preliminary data suggest that *L. infantum* and/or parasite-derived compounds might be potentially exploited as immunomodulatory molecules against inflammation and neurotoxicity in AD. Further investigations aiming at deciphering the exact role of *Leishmania* interfering with the NO signaling pathway in microglia will be undoubtedly needed.

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**References**

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