Nicotinamide Nucleotide Transhydrogenase worsens the clearance ability of mice infected with *Leishmania amazonensis*

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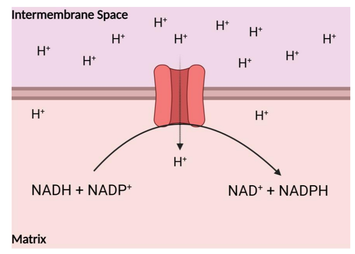
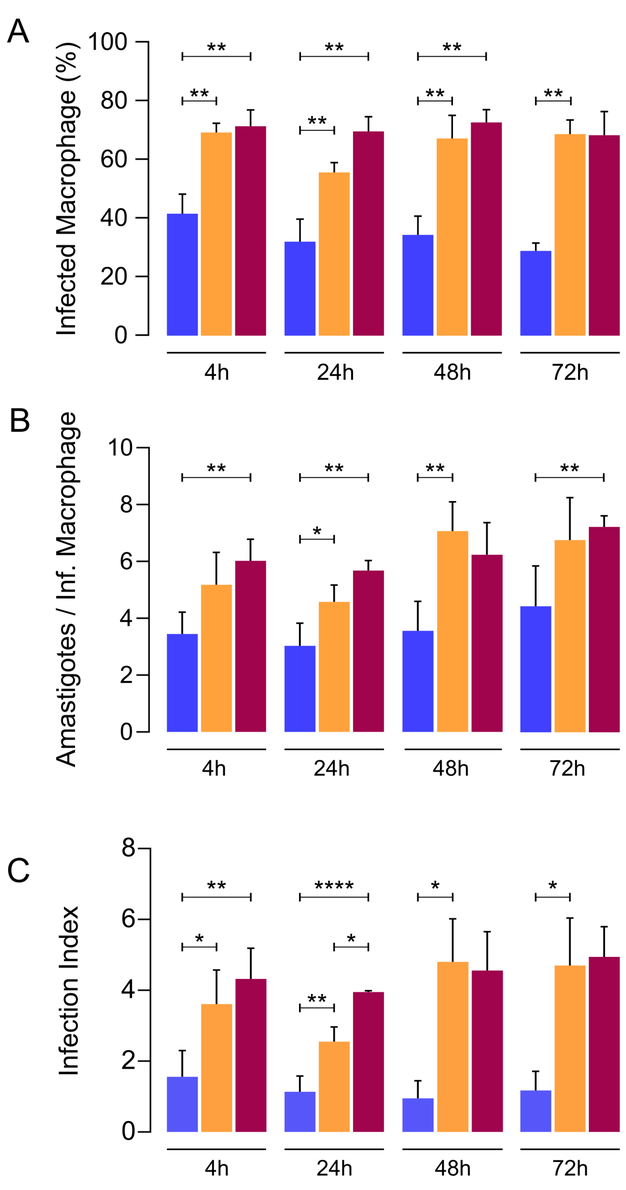
Background

- M1 macrophages are prone to produce ATP via glycolysis
- M2 macrophages tend to use oxidative phosphorylation
- NNT uses the H^+ transmembrane transport from intermembrane space to mitochondrial matrix as a driving force to produce NADPH from an NADH molecule
- NADPH is used to re-reduce glutathione and thioredoxins, promoting mitochondrial H_2O_2 clearance
- BMDM infected with *Leishmania amazonensis* presents a blended M1/M2 phenotype



Is NNT influencing on macrophage-*Leishmania* relationship?

The in vitro infection showed that there is a regulation promoted by NNT.



$Nnt^{-/-}$ macrophages had similar infection rates to $Nos2^{-/-}$, both were higher than B6

The number of amastigotes inside infected macrophages was similar between both knocks out mice.

The infection index showed that NNT absence negatively impacts the parasite clearance of these macrophages.

Figure 1. In vitro infection of bone marrow derived-macrophages infected with *L. amazonensis*. (A) Infected macrophages rate. (B) The number of amastigotes per infected macrophage. (C) Infection Index. Statistics: 2-way ANOVA with Tukey's Comparison post hoc. *, $p \leq 0.05$. **, $p \leq 0.005$. ***, $p \leq 0.0005$. ****, $p \leq 0.0001$. n = 600 macrophages per well, 4 wells per condition.

And *in vivo* infection presented the same behavior

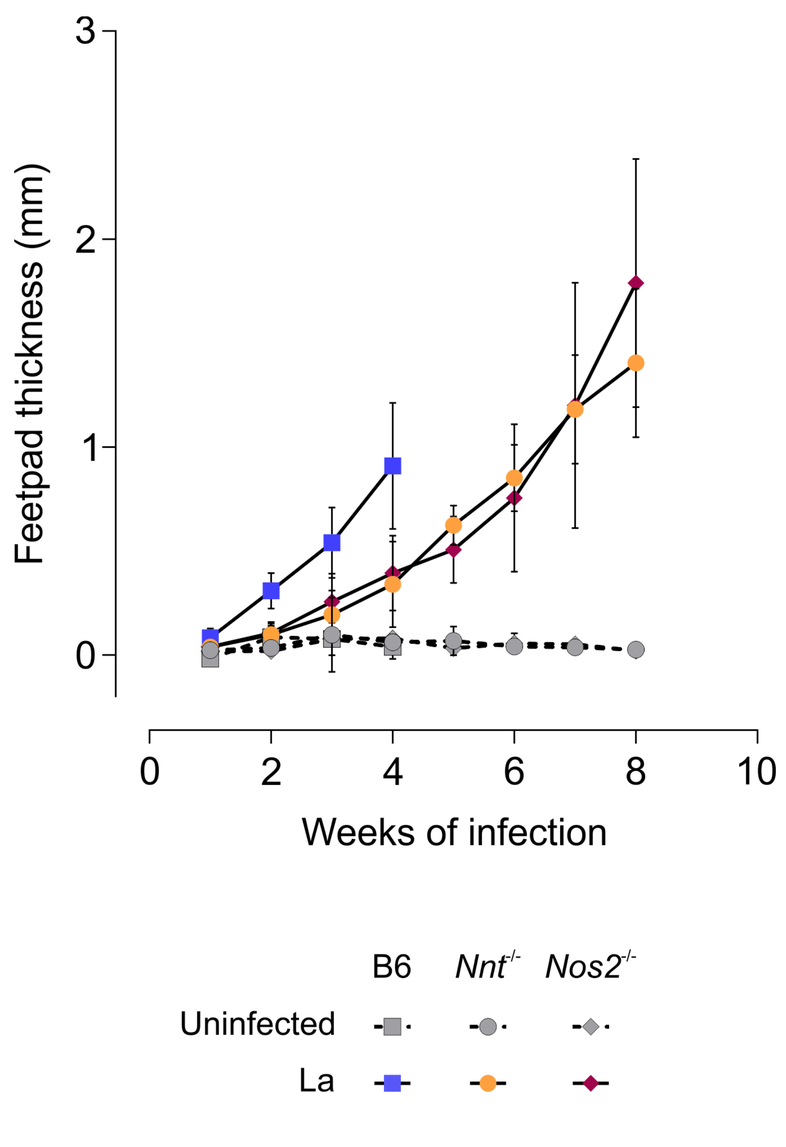
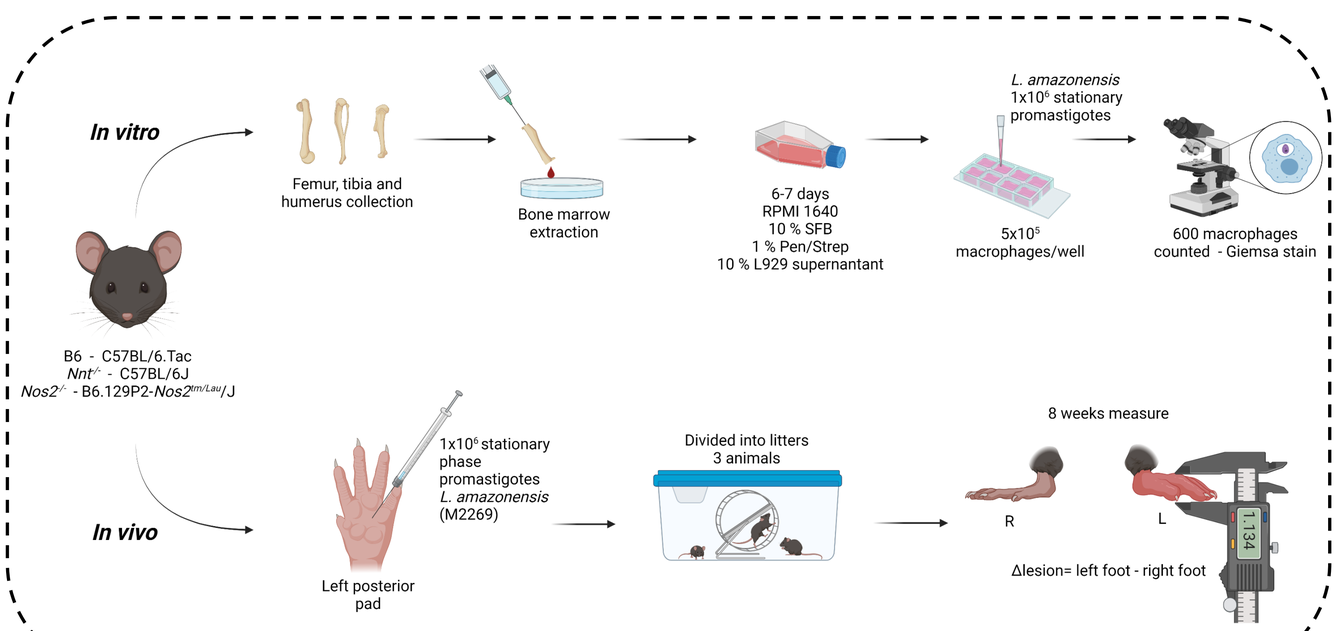


Figure 2. *In vivo* mice infection with *L. amazonensis*. 6-8 week old female were infected with $1x10^6$ stationary phase promastigotes in the left footpad and had weekly thickness measured with a pachymeter. Values in the y axis represent Δ thickness (left footpad – right footpad). PBS 1x was used as the negative control.

Methods



Take home lessons

- Macrophages from an $Nnt^{-/-}$ mouse are similarly susceptible to $Nos2^{-/-}$ when infected with *Leishmania amazonensis*
- The same behavior was observed *in vivo* infection when *Nnt-/-* mice showed the same increase in their footpad lesion size
- These data suggest that the redox state may contribute to a proper macrophage activity
- Further experimentation is needed to paint the whole picture

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