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IL-1β blockade decreased intrauterine inflammation induced by *E. coli* in pregnant Rhesus macaques, but does not reduce rates of preterm birth

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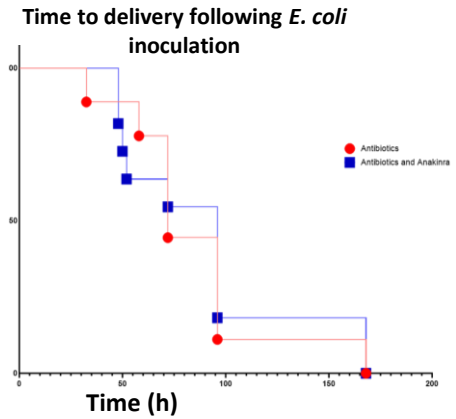
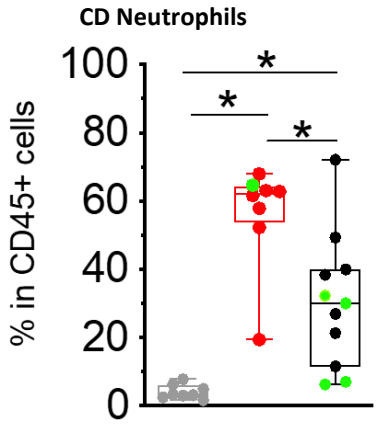
Introduction:

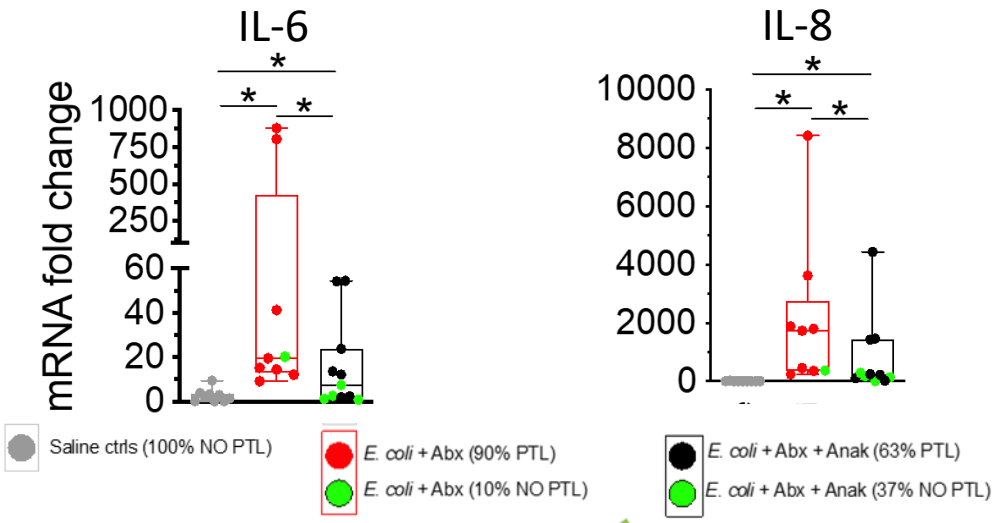
- Intrauterine infection and inflammation (III) is a major cause of preterm birth.
- Intrauterine infection results in a cascade of proinflammatory cytokine release resulting in the recruitment and activation of immune cells leading to inflammation driven preterm birth.
- Key among these cytokines is IL-1β.
- This study aimed to assess the efficacy of IL-1β blockade in a Rhesus macaque (Macaca mulatta) model of preterm IUI.

Methods:

- Ethical Approval – Institutional Animal Care and Use Committee, UCDavis
- Twenty normally cycling adult female Rhesus macaques were time mated and received an ultrasound guided intraamniotic inoculation of 1x10^6 colony forming units of E. coli at approximately 80-85% gestation. The target for inoculation was gestational day 140 (range 135-143) where term is approximately 165 days.
- The macaques were randomised to receive either an antibiotic regimen or the same antibiotic regimen plus a course of the IL-1β antagonist "Anakinra".
- Inoculations were received on Day 0, and the experimental end point was Day 4 (earlier if PTL)







Results:

- All animals had a positive amniotic fluid culture for E. coli 24 hours following inoculation.
- All animals had sterile amniotic fluid cultures 24 hours after antibiotics were commenced.
- 8/9 animals receiving antibiotics alone, and 7/11 animals receiving antibiotics and Anakinra experienced PTL (Fisher's Exact P=0.31 not significant).
- Anakinra significantly reduced the recruitment of neutrophils in to the Chorio-decidua and reduced the expression of IL-6 and IL8 mRNA in the fetal membranes

Conclusion:

- IL-1β blockade with Anakinra significantly reduced the recruitment of neutrophils into the choriodecidua and decreased intrauterine inflammation in the fetal membranes.
- There was a reduction in PTL rates in a small set of animals, but this was not statistically significant.
- Partial efficacy of Anakinra in reducing imflammation at the maternal-fetal interface is encouraging and warrant further investigation
- Work is ongoing assessing the inflammatory response in the fetal brain and CSF, intestine, and lungs.

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