

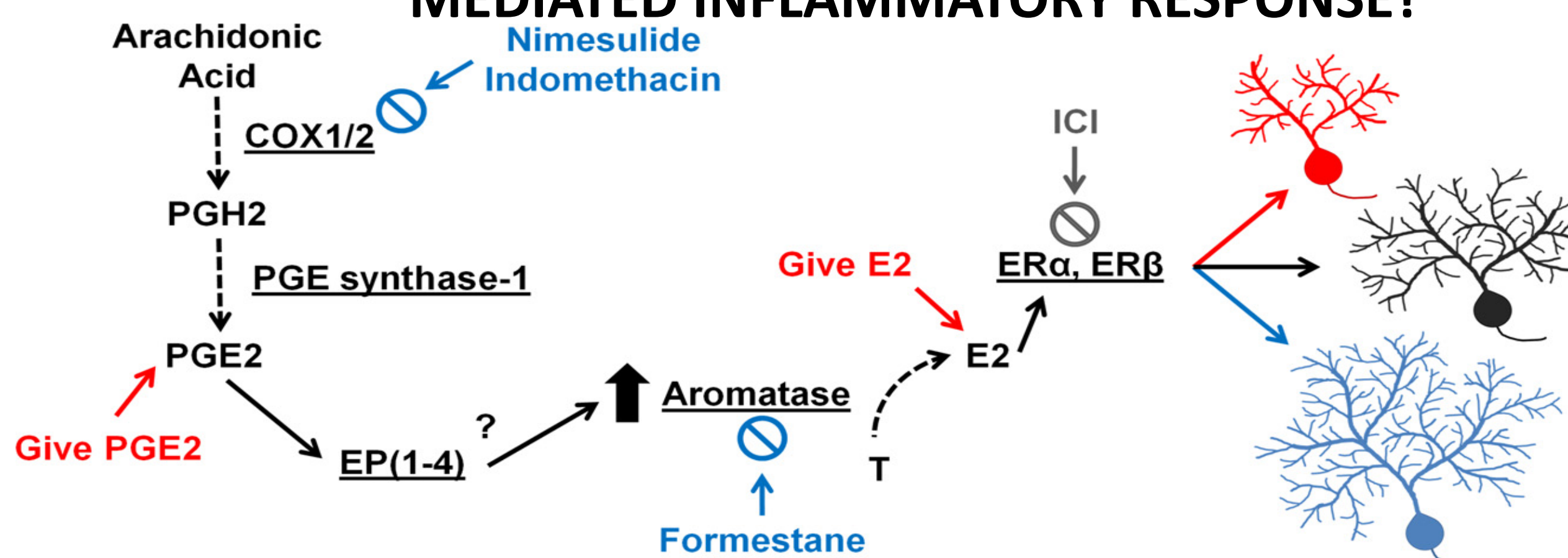
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BACKGROUND

- The cerebellum is one of the first areas to form and the last to fully develop, making it susceptible to developmental perturbations
- Previously, we have shown that LPS, a bacterial mimic, induced inflammation during a critical period in cerebellar development which produced enduring changes to Purkinje neuron growth in males and altered their play behavior later on.
- These changes are mediated by estradiol, produced de novo in the cerebellum, in response to inflammation, via the PGE2-E2 pathway
- LPS induces inflammation via TLR4 signaling. We are curious whether TLR3 induced inflammation has the capacity to induce cerebellar inflammation and trigger the PGE2-E2 pathway just as TLR4 induced inflammation does
- In these studies, we seek to extend our model of LPS induced inflammation into Polyinosinic:polycytidylic acid, PIC, induced inflammation. PIC is a viral mimic that triggers inflammation via a TLR3 mediated pathway. In these studies we characterize the sickness of exposed animals and the cytokine response in cerebellar homogenates and cultured microglia.
- QUESTIONS OF INTEREST:**

- DOES PERIPHERAL PIC TREATMENT INDUCE INFLAMMATION WITHIN THE CEREBELLUM?
- DOES PIC INDUCED INFLAMMATION UTILIZE THE SAME CYTOKINE CASCADE AS LPS INDUCED INFLAMMATION?
- WHAT CYTOKINES ARE INVOLVED IN PIC MEDIATED INFLAMMATORY RESPONSE?

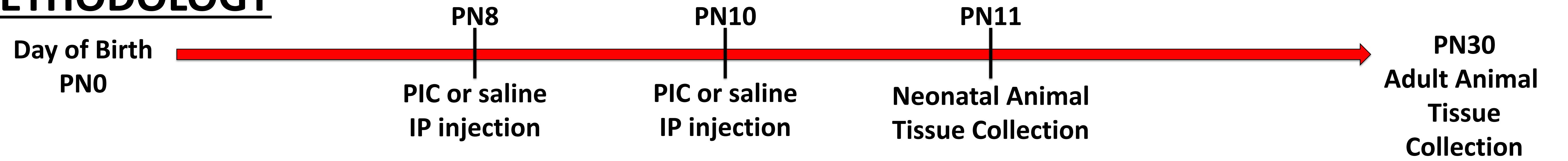


CONCLUSIONS

These data demonstrate that a 5mg/kg dose of PIC administered peripherally, during a sensitive period in cerebellar development, is sufficient to induce sickness while maintaining animal viability. Further, PIC treatment did induce inflammation within the cerebellum as indicated by the presence of CCL5. PIC and LPS stimulation resulted in distinct cytokine profiles, where LPS results in an increase in TNF-A and IL-1B, PIC treatment resulted in CCL5 expression specifically in males. Further work investigating the role that CCL5 plays in this model is warranted.

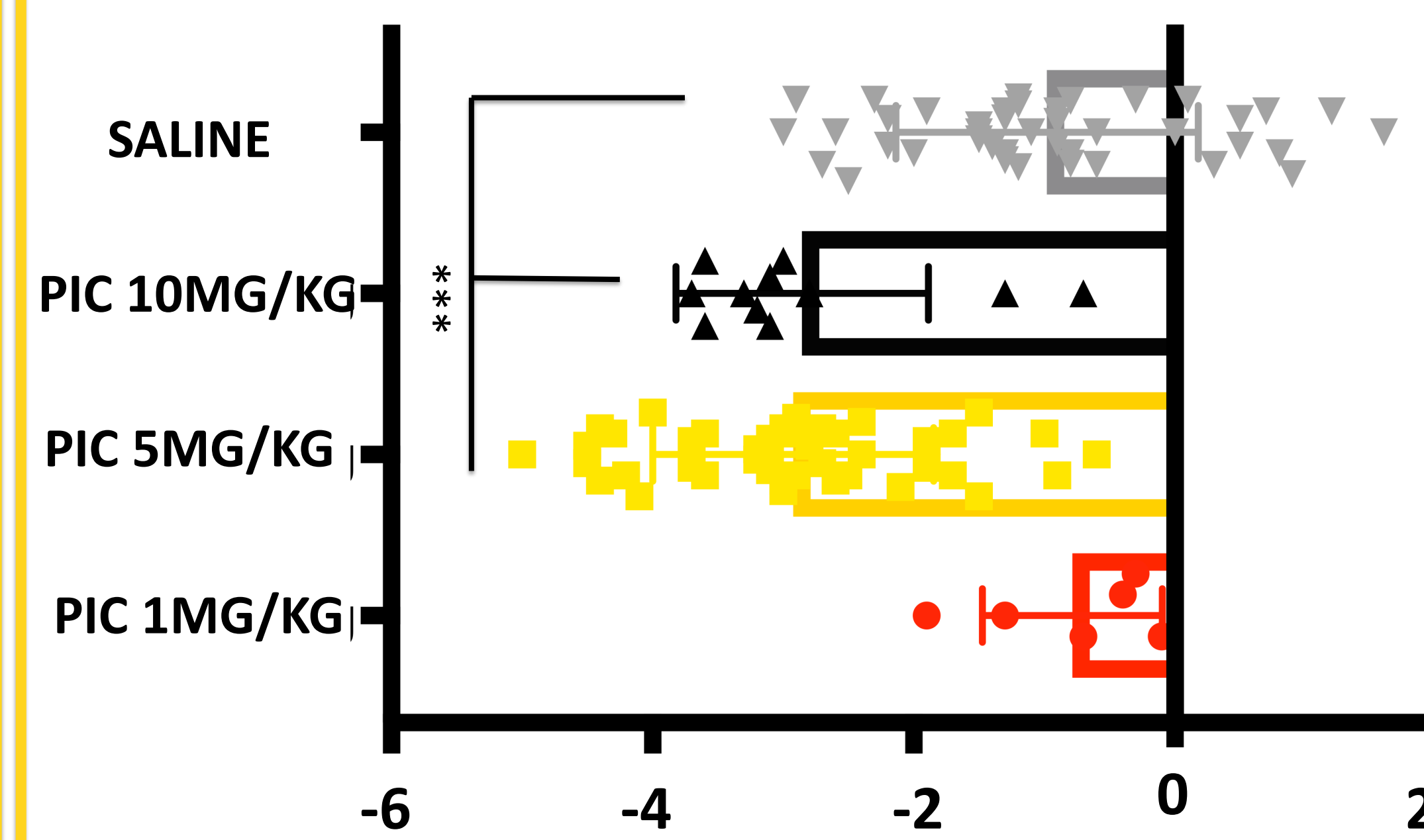
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METHODOLOGY



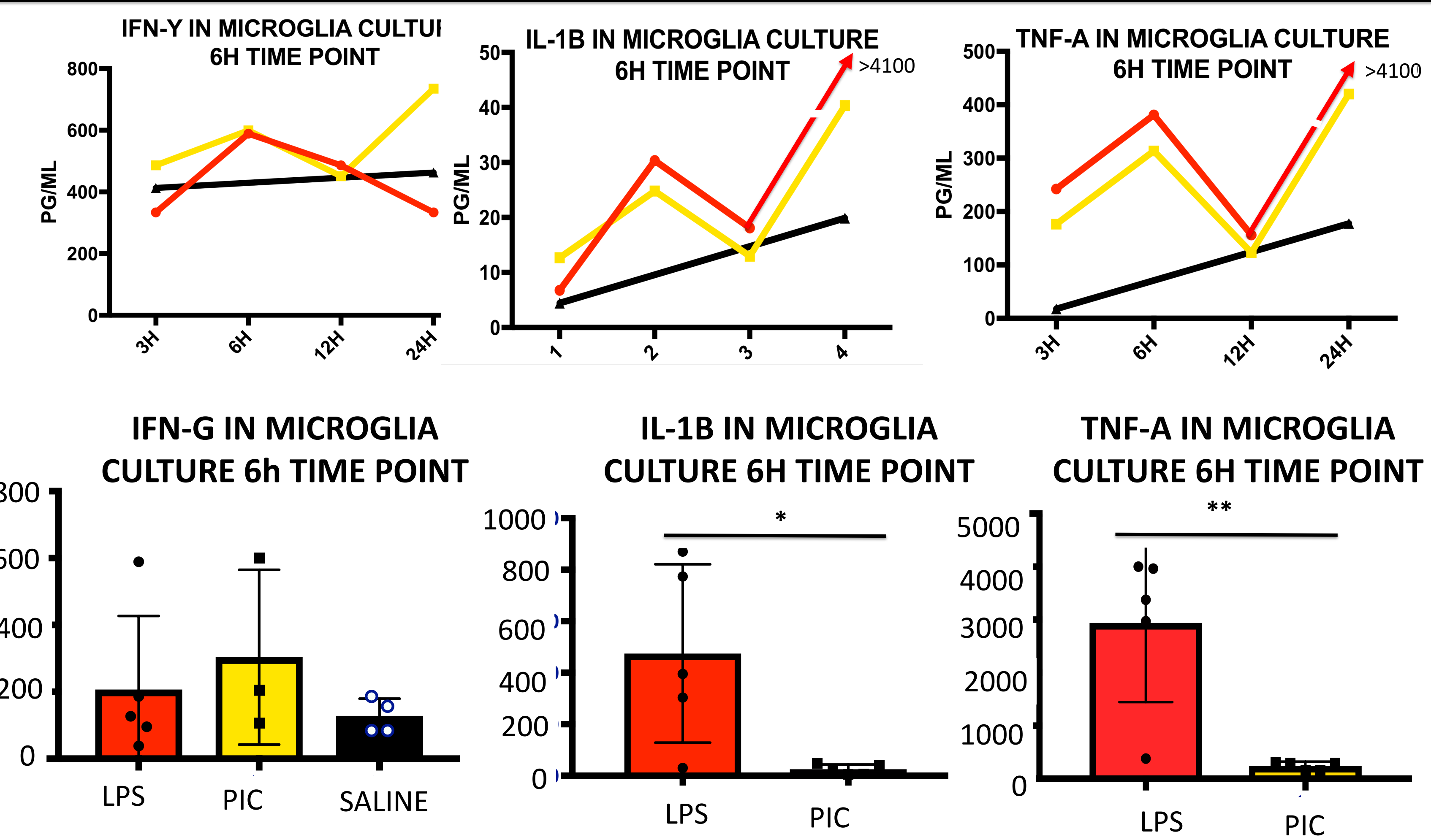
RESULTS

CHANGE IN TEMPERATURE 3H AFTER PIC TREATMENT



CYTOKINES

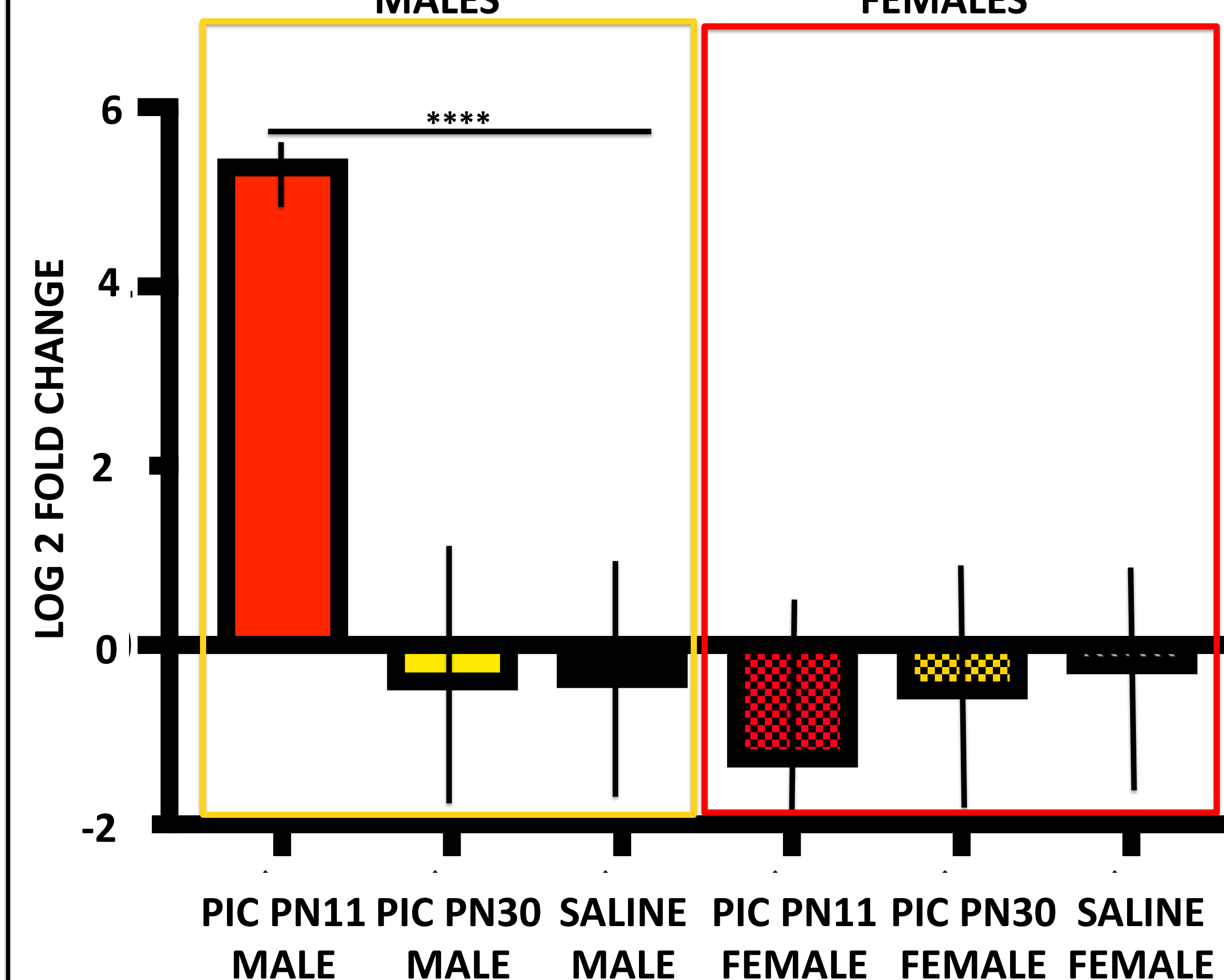
We have previously shown IL-1B and TNF-A are involved in TLR4 mediated cerebellar inflammation. Since PIC induces TLR3 mediated inflammation we wanted to see if PIC and LPS induced inflammation activate similar cytokines and what the time course for cytokine activation is after stimulation.



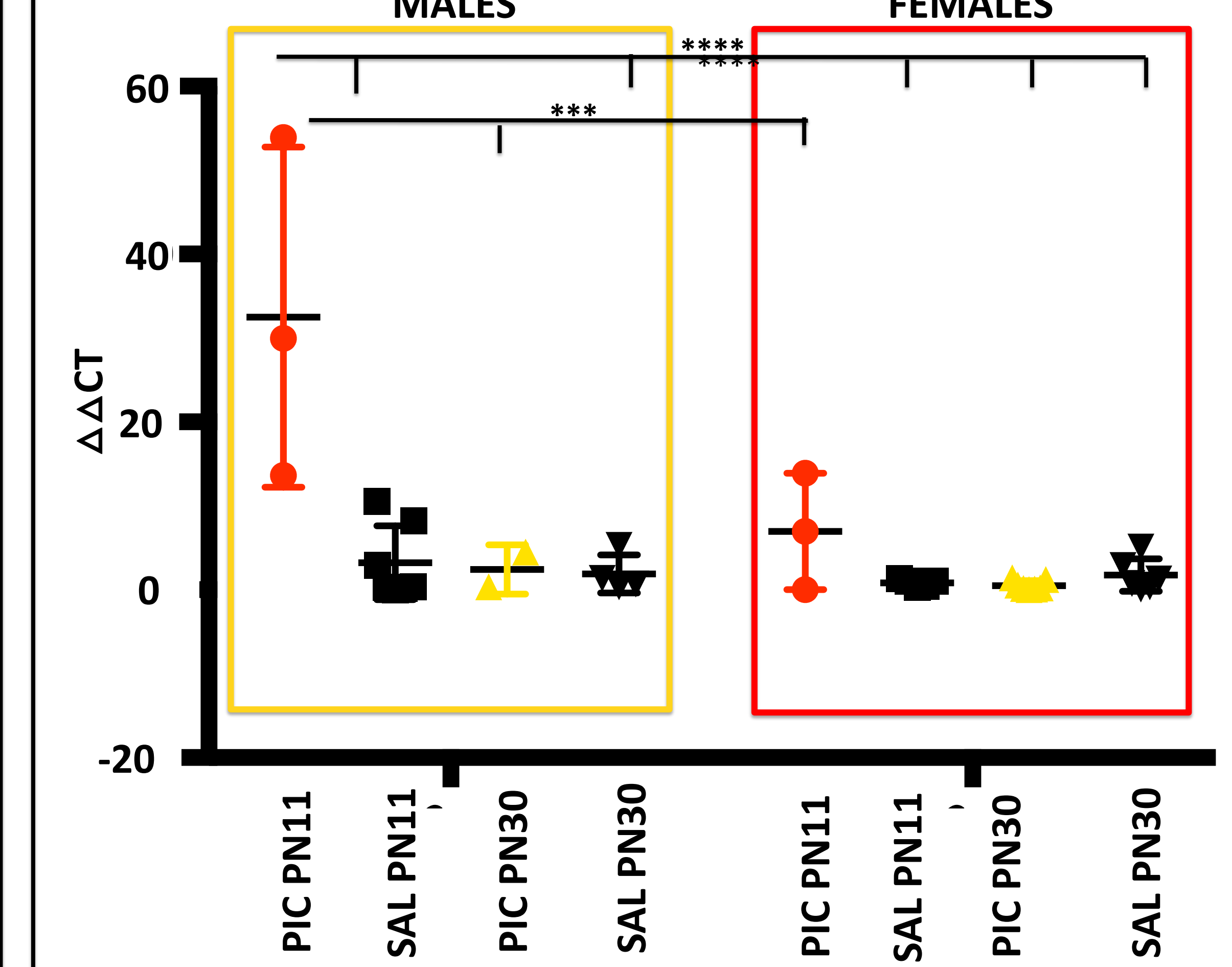
GENE EXPRESSION

Using RNA extracted from cerebellar homogenates we assessed gene expression across several targeted immune, metabolic, and neurotransmitter systems using Nanostring and Polymerase Chain Reaction. Of particular interest to us is that CCL5 (RANTES cytokine) is explicitly expressed in PIC treated PN11 males, not in LPS animals or female PIC animals. CCL5 is a chemotactic cytokine that recruits immune cells to the site of inflammation and has a known protective role in several inflammatory neurological diseases.

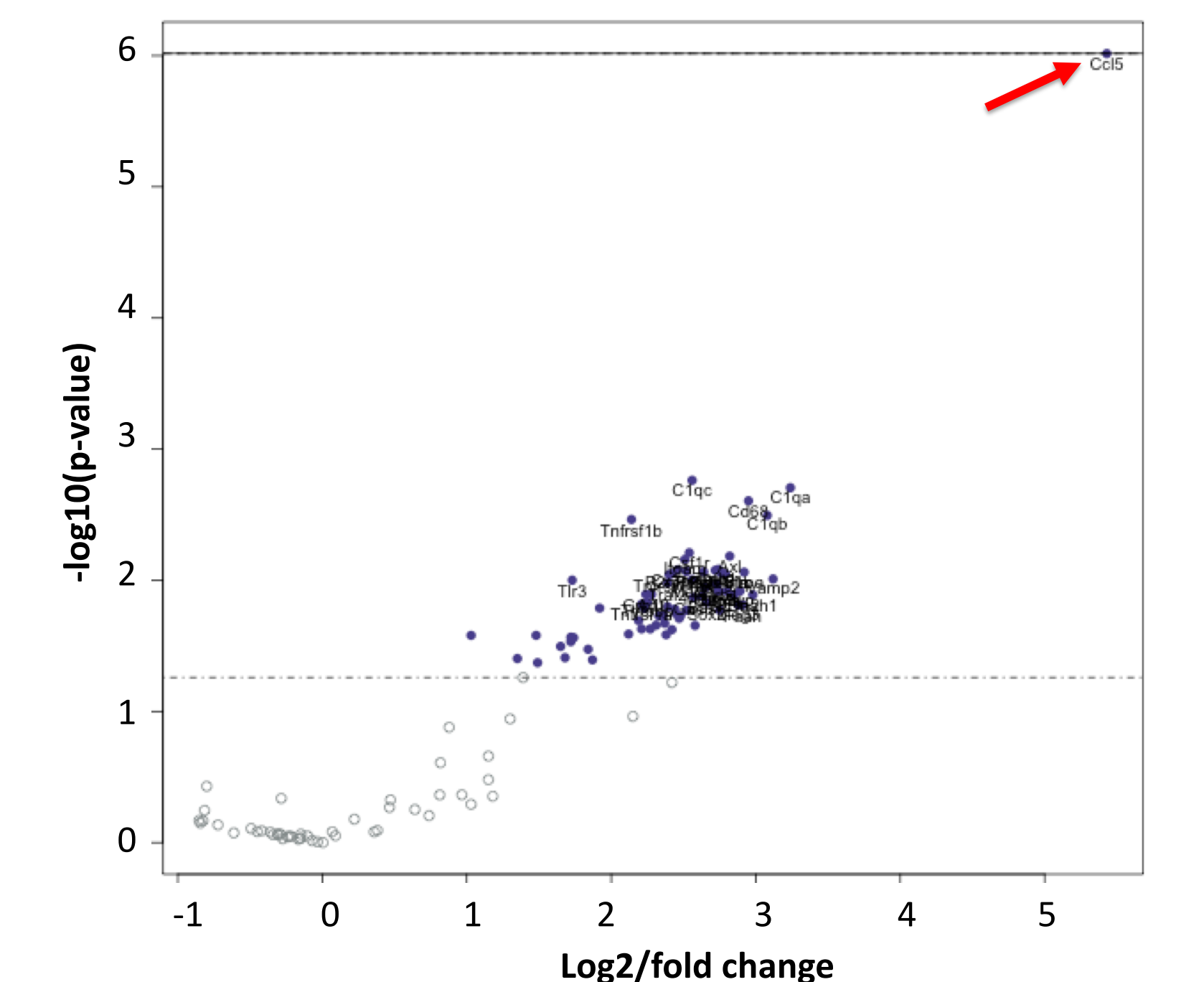
CCL5 Expression via Nanostring



CCL5 Expression via PCR



DIFFERENTIAL GENE EXPRESSION OF PN11 PIC MALE VS PN11 SALINE MALE



DIFFERENTIAL GENE EXPRESSION OF PN11 PIC MALE VS PN11 LPS MALE

