Supervisor Name: Augusto Zani

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Field of Research (2 keywords): Regenerative medicine, Stem cell research

Department: Department of Surgery, University of Toronto

School of Graduate Studies Appointment (IMS, LMP, HIPME etc)? Yes/No: No

If YES, please name:

Project Title: The effects of necrotizing enterocolitis on neonatal neurodevelopment.

Brief Project Description (<300 words):

Background: Necrotizing Enterocolitis (NEC) is a devastating disease of newborn infants, which is still burdened by high mortality and morbidity rates. Clinical studies have shown that 50% of NEC survivors have a degree of neurodevelopmental delay, which is not explained by prematurity alone. Our lab has shown that the intestine of neonatal mice with NEC is severely inflamed, with marked neutrophil infiltration. Moreover, we have recently observed that the brain of neonatal mice with NEC shows signs of inflammation (increased cytokine levels), significant activated cerebral immune response (microgliosis) and architectural changes in the brain (reduced number of mature neurons, oligodendrocytes and neural progenitor cells).

Hypothesis: The circulating cytokines from the inflamed intestine cross the blood-brain-barrier (BBB) and activate a cerebral immune response (microgliosis) that eventually causes damage of cerebral cells (mature neurons, oligodendrocytes, and neural progenitor cells).

Objectives:
1) To determine whether circulating cytokines cross BBB during NEC;
2) To test if depleting the cerebral immune response ablates brain damage.

Methods and role of the student:
1) To test BBB integrity, the student will use histology following Evan’s blue stain, and cell sorting (FACS) to interrogate the presence of circulating monocytes (sign of leaky BBB);
2) To evaluate the role of the cerebral immune response during NEC, the student will conduct immunofluorescence, qRT-PCR, and Western blot on the brain of NEC mice, which received a pharmacological agent (CSF1R inhibitor) that depletes microglia in vivo. The student is not expected to conduct in vivo animal experiments, unless an interest is specifically expressed.

Significance of the research: This study will advance our knowledge on the pathogenesis of NEC associated brain damage. If our hypothesis is confirmed, further studies will focus on identifying potential targets in the gut-brain axis that could be blocked to prevent or attenuate brain damage during NEC.