UNIVERSITY OF TORONTO
LESLIE DAN FACULTY OF PHARMACY

GRADUATE DEPARTMENT OF PHARMACEUTICAL SCIENCES

TOXICOLOGY GROUP TRAINEE SEMINAR PROGRAM

Wednesday, October 14, 2015, 2:10–3:30 p.m.

Room 850, 144 College Street

Title: **Development of an Animal Model to Investigate the Mechanism of Idiosyncratic Clozapine-Induced Agranulocytosis**

Trainee: **ALEX JOHNSTON**

Supervisor: Dr. Jack Uetrecht

Advisors: Dr. Carolyn Cummins, Dr. Phillippe Poussier

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ABSTRACT

Clozapine (CLZ) is a very effective antipsychotic agent, but its use is limited by the fact that it causes agranulocytosis in 0.1-1% of patients. Although most patients do not develop agranulocytosis, most do develop transient paradoxical neutrophilia and an increase in cytokines such as IL-6. A recent paper also reported an increase in peripheral monocytes that precedes the increase in neutrophils (1). In addition, we found that treatment of THP-1 cells (a human monocyte cell line) with clozapine led to inflammasome activation with release of IL-1ß. This suggests that most patients do have an immune response to the drug, but in most patients this resolves without resulting in agranulocytosis, presumably via immune tolerance. If we could reproduce this immune response in animals it would allow us to study the mechanism by which clozapine induces an immune response and this could help us understand the mechanism of idiosyncratic agranulocytosis. Mice are very sensitive to the neurologic effects of CLZ. The dose of CLZ that they tolerate is limited, and they do not respond with neutrophilia. In contrast, treatment of rats with CLZ (0.5 mg/ml + 0.1 g sucrose in drinking water) results in clinically relevant serum concentrations of CLZ (0.2 µg/ml), and this did result in neutrophilia. In addition, there was an increase in the % peripheral monocytes (CD3- and CD11b/c+) from 12 to 26%. There also appeared to be an increase in NK cells. Given the result with THP-1 cells, we postulate that these effects are due to activation of monocytes with the production of IL-1ß; however, we were not able to detect an increase in serum IL-1ß in rats. Further studies will be performed to phenotype the monocytes in the rat model and to determine the mechanism by which their numbers are increased. This research was supported by grants from the Canadian Institutes of Health Research.

1. Lee, J., Takeuchi, H., Fervaha, G., Powell, V., Bhaloo, A., Bies, R., & Remington, G. (2015). The Effect of Clozapine on Hematological Indices: A 1-Year Follow-Up Study. Journal of clinical psychopharmacology. 35(5): 510-516.