UNIVERSITY OF TORONTO
LESLIE DAN FACULTY OF PHARMACY

GRADUATE DEPARTMENT OF PHARMACEUTICAL SCIENCES

TOXICOLOGY GROUP TRAINEE SEMINAR PROGRAM

Wednesday, April 15, 2015, 2:10–3:30 p.m.

Room 850, 144 College Street

Title: **Investigating the Skin Rash Caused by Trimethoprim**

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Supervisor: Jack Uetrecht

Advisors: Donald Weaver and Mark Nitz

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ABSTRACT:

Idiosyncratic drug reactions (IDRs) are unexpected adverse reactions that do not occur in most people and do not involve the known pharmacological effects of the drug. The mechanism of these reactions are not well understood. Circumstantial evidence suggests that most IDRs are caused by chemically reactive metabolites of drugs that covalently bind to proteins. Such covalent binding can be detected by antibodies that recognize this binding. The most common type of IDR is skin rashes; however, there are few metabolic enzymes in skin and given their reactivity, presumably reactive metabolites must be formed close to where they bind. Recently, nevirapine a non-nucleoside reverse transcriptase inhibitor, which is associated with a high incidence of skin rash, was shown to covalently bind to proteins in the skin. Nevirapine-induced skin rash was shown to be caused by a reactive benzylic sulfate formed in the skin. Although metabolism of drugs in the skin is limited, one exception is sulfotransferase activities. Other drugs may also cause drug-induced skin rash by a similar mechanism. Trimethoprim (TMP) is an effective antibacterial and anti-malarial agent, but it can cause IDRs that range from mild skin rashes to toxic epidermal necrolysis. TMP is known to be oxidized to a benzylic alcohol, and this has the potential to form a reactive sulfate analogous to nevirapine. TMP-ketone metabolite was successfully prepared by oxidizing TMP with manganese oxide, followed by reduction of the ketone using sodium borohydride to the hydroxy-TMP metabolite. Hydroxy-TMP was used to prepare the sulfate metabolite via sulfur-trioxide triethylamine sulfation, and the reactivity of the sulfate is to be tested. An antibody against trimethoprim-modified proteins will also be produced to test whether it covalently binds to proteins in the skin.