UNIVERSITY OF TORONTO
LESLIE DAN FACULTY OF PHARMACY

TOXICOLOGY GROUP TRAINEE SEMINAR PROGRAM

Wednesday, January 13, 2016, 2:10–3:30 p.m.

Room 850, 144 College Street

Title: **Influence of sex on hepatotoxic and immune responses in a model of chemical-induced liver carcinogenesis in the mouse**

Trainee: **DANIEL HANNA**

Supervisor: Dr. Denis M. Grant

Advisory committee: Drs. Dana J. Philpott, Jack Uetrecht and Peter G. Wells

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ABSTRACT:

The incidence of liver cancer is 3-fold higher in men than in women. Mice show a similar male predominance in liver tumor incidence after exposure to liver carcinogens such as 4-aminobiphenyl (ABP) or diethylnitrosamine (DEN), while chemical-induced DNA damage does not differ between sexes. Chronic inflammation is now recognized as a significant risk factor for many cancers, including that of the liver. Adult male mice exposed to DEN show greater DEN-induced acute hepatotoxicity and inflammation than female mice, which appears to be estrogen-dependent. However, standard tumor induction protocols using postnatal exposure of immature mice to carcinogens do not produce either hepatotoxicity or inflammation. However, it is not known whether these responses develop chronically, and whether sex hormones are involved. To investigate this, we exposed male and female mice postnatally to either ABP or DEN and sacrificed them at a range of times up to the point at which tumor growth is normally assessed, to determine whether hepatotoxic and inflammatory responses differ between sexes and if these responses promote hepatic proliferation. So far we have seen no effect of postnatal ABP exposure on chronic body weight gain, hepatotoxicity or hepatic proliferation. On the other hand, DEN caused a significantly greater gain in body weight only in male mice, but did not produce any chronic hepatotoxicity in either sex. These results suggest that neither ABP nor DEN cause any detectable hepatotoxicity and that chemical specific factors may be responsible for the difference observed in weight gain in males.