UNIVERSITY OF TORONTO
LESLIE DAN FACULTY OF PHARMACY

TOXICOLOGY GROUP TRAINEE SEMINAR PROGRAM

Wednesday, September 17, 2014, 2:10–3:30 pm

Room 1210, 144 College Street

Title: **Exposure to rufinamide and risks of CNS adverse events in drug-resistant epilepsy: A systematic review and meta-analysis of randomized placebo-controlled trials**

Trainee: **ABDULAZIZ M.S. ALSAAD**, Ph.D. Candidate

Supervisor: Dr. Gideon Koren

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ABSTRACT:

Purpose: Epilepsy is a complex disease necessitating continuous development of new therapeutic strategies to encounter drug-resistant cases. Among the new adjuvant antiepileptic drugs, rufinamide is considered a novel compound that is structurally distinct from other antiepileptic drugs. It is used to treat partial-onset seizures and seizures associated with Lennox-Gastaut syndrome in adult and children. Although the effectiveness of rufinamide has been studied, to date, there has been no attempt to systematically evaluate the risks of rufinamide's adverse events.

Method: We performed a quantitative risk analysis of the central nervous system (CNS) adverse events of rufinamide from all randomized, double blind, add-on, and placebo-controlled trials. Of the 886 publications reviewed, 99 papers were retrieved and five articles met the inclusion criteria. Around 1252 patients were included in this meta-analysis.

Results: Our study showed that exposure to rufinamide is associated with a significant increase in risk of somnolence (RR 1.87; 95% CI 1.33 to 2.62; P=0.0003), dizziness (2.66; 2.00 to 3.55; P=0.00001), fatigue/lethargy (2.14; 1.57 to 2.91; P=0.01), and headache (1.28; 1.02 to 1.59, P= 0.03). In addition, exposure to rufinamide was associated with higher treatment discontinuation rates as compared to placebo (2.65; 1.74 to 4.03; P=0.00001).

Conclusions: The risk of CNS adverse events appears to be increased in patients exposed to rufinamide as well as the treatment discontinuation rates. However, although statistical association was significant, additional studies are required to confirm clinical significance of these findings, as most reports involved mild to moderate adverse events. Ultimately, to help in clinical decision-making process, this study would be an important consideration when choosing the appropriate adjuvant therapy for the next patient with epilepsy, with Lennox-Gastaut syndrome or not.

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Title: **Regulation of cisplatin-induced programmed cell death *in vivo***

Trainee: **MAYA LATIF**, M.Sc. Candidate

Co-Authors: Yanshan Cao, Kelvin Hui, Zoe Winterton-Perks, Andrew Elia

Supervisor: Dr. Jeffrey Henderson

Advisors: Dr. Micheline Piquette-Miller and Dr. Razq Hakem

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ABSTRACT:

Cisplatin represents the canonical member of a group of platinum-based chemotherapeutic agents that have shown great efficacy in the treatment of a variety of malignancies including sarcomas, lymphomas, germ cell tumours and several carcinoma subtypes. Despite this, the clinical utility of platinum-containing compounds faces significant limitations due to side effects such as neuro-, oto-, and nephrotoxicity that result from induction of cell death in healthy proliferating tissues. The mechanism of cisplatin-mediated cell death has long been thought to involve interactions of the hydrated form of the drug with cellular nucleophiles, resulting in the formation of inter- and intra-strand crosslinks between DNA purine bases. It is widely held that these DNA-platinum adducts trigger DNA repair processes, cell cycle arrest, and ultimately p53-mediated cell death.

To examine the mechanism of cisplatin toxicity in greater detail, the developing murine embryo was utilized as a model of rapid cellular proliferation. *In vivo* treatment with cisplatin at dosages below those used clinically in humans resulted in widespread cellular injury in a variety of solid organs. In wild-type animals, this injury was characterized by p53 and gamma H2AX phosphorylation, induction of caspase-3 and caspase-7, cleavage of the caspase target poly (ADP-ribose) polymerase (PARP), and formation of TUNEL-positive DNA strand breaks. Analysis of cellular morphology by electron microscopy revealed formation of apoptotic bodies, indicating that under normal circumstances cisplatin promotes cell death through the induction of apoptosis.

To define the mechanistic nature of this cell death, levels of cellular injury *in vivo* following cisplatin treatment were examined in mice carrying genetic modifications of key genes in apoptotic pathways. Strikingly, animals homozygous for a null mutation of caspase-3 exhibit a complete inhibition of cisplatin-dependent cell death at 24 hours following treatment in a wide variety of tissues. This effect was observed despite the detection of caspase-7 activity following cisplatin treatment in both wild-type animals and those lacking caspase-3, demonstrating a novel functional variance between these two central executioner caspases. These findings have important clinical implications toward maintenance of both normal and malignant cells in a variety of tissues in the presence of cisplatin.