UNIVERSITY OF TORONTO
LESLIE DAN FACULTY OF PHARMACY

GRADUATE DEPARTMENT OF PHARMACEUTICAL SCIENCES

TOXICOLOGY GROUP TRAINEE SEMINAR PROGRAM

Wednesday, May 13, 2015, 2:10–3:30 p.m.

Room 850, 144 College Street

Title: **Examination of Programmed Cell Death Signal Regulation Via *CRISPR*-Mediated Targeted Network Analysis**

Trainee: **CHESARAHMIA DOJO SOEANDY**

Supervisor: Dr. Jeffrey Henderson

Advisors: Drs. Peter G. Wells and Cindi Morshead

==========

ABSTRACT:

Programmed cell death (PCD) is a core developmental process involved in an array of normal and pathologic functions in all metazoans. There are several recognized forms of PCD, namely: apoptosis, necroptosis and autophagy; each of which exhibits unique morphologic and molecular features. Abnormal regulation of these different forms of PCD is, in turn, known to occur in cancers and neurodegenerative disorders, as well as play a vital role in acute injury states such as spinal cord injury and stroke. Understanding the molecular mechanisms which regulate PCD is therefore critical to enhancing functional recovery of the central nervous system following injury. In order to identify key regulator interactions which control this process, I have created a series of single and combinatorial null mutations of 18 key PCD (apoptotic, necroptotic and autophagic) members in embryonic stem (ES) cells through the use of a novel genomic engineering technique known as CRISPR (clustered regularly interspaced short palindromic repeats). These ES mutants will subsequently be differentiated into cortical neurons, and both cell types exposed to various independent triggers of programmed cell death (stroke-related hypoxia and NMDA exposure, chemotherapeutic exposure and oxidative stress). Thus, although much has been determined about the biochemical properties of each individual pathway member, the use of this method allows one to examine how the various members of the pathway *work together*. Consequently, this study will enhance our knowledge of this fundamental cellular process involved in neural injury and thus help to direct future small molecule development.