

Candidacy Exam Project Outlines

Primary Proposal:

Hematopoietic cancers and *NUP98* fusions: determining common mechanisms of malignancy

Nup98 has several cellular functions, participating in RNA and protein export, gene expression, immune response and cell cycle progression. In mice *NUP98* is essential for animal viability, and rearrangements of *NUP98* lead to hematopoietic malignancies. *NUP98* gene fusions have also been detected in human hematopoietic cancers, where it indicates poor prognosis with worse survival. At least 28 different partner genes fused to *NUP98* have been described. The fusion proteins encoded always retain the N-terminal portion of Nup98, indicating an important function for this domain in hematopoietic carcinogenesis. In this project I would like to define common mechanisms by which these different nup98 fusions lead to malignancy. Using a high-throughput approach I'll identify proteins, DNA and RNA sequences interacting with these nup98 fusions as well as their effects in gene expression and cell cycle regulation. Pathways commonly affected by different nup98 fusions will be chosen for further investigation in a search for novel therapeutic targets.

Alternate Proposal:

Elucidating Nup98's function in DNA damage repair in humans

In *Saccharomyces cerevisiae* Nuclear Pore Complexes (NPCs) play an important role in DNA damage repair. The Nup84 complex shows genetic interactions with components from the non-homologous end joining (NHEJ) machinery and mutants of these nucleoporins display increased DNA double strand breaks. Nup145 is a component of the Nup84 complex, its homologue in *Aspergillus nidulans* is sonB^{nup98}. A mutant presenting a single amino acid change in this protein also shows increased sensitivity to DNA damage. Nup98 is the human homologue of Nup145 and sonB^{nup98}. In my recent results identifying Nup98 protein interactions in human cells, I have detected an interaction between DNA dependent protein kinase (DNA-PK) and Nup98. DNA-PK is a component of the NHEJ DNA repair pathway in humans, the same DNA repair mechanism affected by the Nup84 complex in yeast. In this project I would like to determine the molecular pathways connecting Nup98 and NHEJ DNA repair in humans.

Exam: 20 December 2011 – 2:30 p.m. TELUS Centre 145

Examining Committee: Dr. Rick Wozniak, Dr. Paul Melançon, Dr. Mark Glover, Dr. Tom Hobman, and Dr. Andrew MacMillan