



**PROGRAMME**

The Final Oral Examination  
For the Degree of

**MASTER'S OF SCIENCE**  
(Medical Genetics)

**RACHEL ELVES**

B. Sc. University of British Columbia, 2004

Tuesday, August 12, 2008, 9:30am

Room 5510, Life Science Centre, 2350 Health Sciences Mall,  
Vancouver, B.C., V6T 1Z3, Canada

**"Consequences Of Mitotic Loss Of Heterozygosity On Genomic  
Imprinting In Mouse Embryonic Stem Cells"**

**EXAMINING COMMITTEE**

Chair:

Dr. Dixie Mager

Supervisory Committee:

Dr. Louis Lefebvre, Research Supervisor (Medical Genetics)

Dr. Carolyn Brown (Medical Genetics)

University Examiner:

Dr. Angela Brooks-Wilson (Medical Genetics)

## ABSTRACT

Epigenetic differences between maternally inherited and paternally inherited chromosomes, such as CpG methylation, render the maternal and paternal genome functionally inequivalent, a phenomenon called genomic imprinting. This functional inequivalence is exemplified with imprinted genes, whose expression is parent-of-origin specific. The dosage of imprinted gene expression is disrupted in cells with uniparental disomy (UPD), which is an unequal parental contribution to the genome. I have derived mouse embryonic stem (ES) cell sub-lines with maternal UPD (mUPD) for mouse chromosome 6 (MMU6) to characterize regulation and maintenance of imprinted gene expression.

The main finding from this study is that maintenance of imprinting in mitotic UPD is extremely variable. Imprint maintenance was shown to vary from gene to gene, and to vary between ES cell lines depending on the mechanism of loss of heterozygosity (LOH) in that cell line. Certain genes analyzed, such as *Peg10*, *Sgce*, *Peg1*, and *Mit1* showed abnormal expression in ES cell lines for which they were mUPD. These abnormal expression levels are similar to that observed in ES cells with meiotically-derived full genome mUPD (parthenogenetic ES cells).

Imprinted CpG methylation at the *Peg1* promoter was found to be abnormal in all sub-lines with mUPD for *Peg1*. Two cell sub-lines which incurred LOH through mitotic recombination showed hypermethylation of *Peg1*, consistent with the presence of two maternal alleles. Surprisingly, a cell sub-line which incurred LOH through full chromosome duplication/loss showed hypomethylation of *Peg1*. The levels of methylation observed in these sub-lines correlates with expression, as the first two sub-lines showed a near-consistent reduction of *Peg1*, while the latter showed *Peg1* levels close to wild-type.

Altogether these results suggest that certain imprinted genes, like *Peg1* and *Peg10*, have stricter imprinting maintenance, and as a result show abnormal expression in UPD. This strict imprint maintenance is disrupted, however, in UPD incurred through full chromosome duplication/loss, possibly because of the trisomic intermediate stage which occurs in this mechanism.

## BIOGRAPHICAL NOTES

**Born:** April 2, 1980, Whitehorse, Yukon  
**Academic Studies:** B. Sc. University of British Columbia, 2004  
**Current Position:** MSc candidate, UBC

## GRADUATE STUDIES

**Field of Study:** Genomic Imprinting in Mouse

## Courses

MEDG 505 Genome Analysis  
MEDG 515 Mammalian Developmental Genetics  
MEDG 520 Advances in Human Molecular Genetics  
MEDG 530 Human Genetics  
MEDG 545 Current Topics in Medical Genetics  
MEDG 548 Directed Studies

## Instructors

Drs. S. Jones & P. Hietler  
Drs. D. Juriloff & M. Harris  
Dr. A. Brooks-Wilson  
Dr. L. Clarke  
Dr. C. Brown  
Dr. L. Lefebvre

## AWARDS

2008 CSBMCB Epigenetics and Chromatin Dynamics Meeting Travel Award  
2005 UBC Medical Genetics Entrance Scholarship

## PRESENTATIONS

Eives, R., Lefebvre, L. Consequences of Mitotic LOH on Genomic Imprinting in Mouse ES Cells. CSBMCB Epigenetics and Chromatin Dynamics Meeting, Banff, Alberta, March 6 - 9, 2008.

## SUPERVISORY COMMITTEE

Dr. Louis Lefebvre, Research Supervisor (Medical Genetics)  
Dr. Dixie Mager (Medical Genetics)  
Dr. Carolyn Brown (Medical Genetics)