

SUPERVISORY COMMITTEE

Dr. Xiaoyan Jiang, Research Supervisor (Medical Genetics)
Dr. Keith Humphries (Medicine; Medical Genetics; Pathology & Laboratory Medicine)
Dr. Gregg Morin (Medical Genetics)

PROGRAMME

The Final Oral Examination
For the Degree of

MASTER'S OF SCIENCE
(Medical Genetics)

ERIN KENNAH

B. Sc., University of British Columbia, 2005

Wednesday, June 25, 2008, 12:30 – 3:00 PM
8th Floor Seminar Room, BC Cancer Research Center, 675 West 10th Ave

**"Identification of Differentially Expressed Genes in
AHL-1-Mediated Leukemic Transformation in Human Cutaneous
T-cell Lymphoma"**

EXAMINING COMMITTEE

Chair:

Dr. Dixie Mager (Medical Genetics)

Supervisory Committee:

Dr. Xiaoyan Jiang, Research Supervisor (Medical Genetics)

Dr. Gregg Morin (Medical Genetics)

University Examiner:

Dr. Pamela Hoodless (Medical Genetics)



UNIVERSITY OF BRITISH COLUMBIA

ABSTRACT

The oncogene *Ahl-1* was recently identified through provirus insertional mutagenesis in murine leukemias and lymphomas. Its involvement in human leukemogenesis is demonstrated by gross perturbations in its expression in several leukemic cell lines, particularly in cutaneous T-cell lymphoma (CTCL) cell lines (Hut 78 and Hut 102). Hut 78 is derived from a patient with Sezary syndrome, a common leukemic variant of the human CTCL mycosis fungoides. Aberrant expression of *AHL-1* mRNA and protein has been found in CD4⁺CD7⁺ leukemic Sezary cells from patients with Sezary syndrome. Moreover, stable suppression of *AHL-1* using retroviral-mediated RNA interference in Hut 78 cells inhibits their transforming activity *in vitro* and *in vivo*.

In an effort to identify genes involved in *AHL-1*-mediated leukemic transformation in CTCL, microarray analysis was performed to compare six RNA samples from *AHL-1* suppressed Hut 78/sh4 cells to five samples from Hut 78 control cells. Limma and dChip analyses identified 218 and 95 differentially expressed genes, respectively, using a fold change criteria of > 2 and a p-value threshold of ≤ 0.001 . After evaluation of both analyses, 21 genes were selected based upon interesting structural and functional information, specificity to hematopoietic cells or T-cells, and previous connections to cancer. Expression patterns of these 21 genes were validated by qRT-PCR with p-values < 0.05 ranging from 1.97×10^{-10} to 6.55×10^{-3} , with the exception of *BRDG1* at 5.88×10^{-2} .

The observed up-regulation of both *BIN1* and *HCK* in *AHL-1* suppressed Hut 78/sh4 cells as compared to control cells further confirmed at the protein level. The tumor suppressor *BIN1* is known to physically interact with c-MYC, which also exhibits differential protein expression in these cells. Characterization of *BIN1* identified 4 isoforms all of which contain exon 10 and demonstrate alternative splicing of exons 12A and 13. Additionally, qRT-PCR results from primary Sezary samples indicate there is clinical significance in the expression changes detected for *BIN1*, *HCK*, *REPS2*, *BRDG1*, *NKG7* and *SPIB*. These findings identify several new differentially expressed genes that may play critical roles in *AHL-1*-mediated leukemic transformation of human CTCL cells.

BIOGRAPHICAL NOTES

Born: February 8th, 1982, North Vancouver
Academic Studies: B. Sc. University of British Columbia, 2005
Current Position: M. Sc. candidate, UBC

GRADUATE STUDIES

Field of Study: Cancer genetics

Courses

MEDG 520 Advances in Human Molecular Genetics

MEDG 521 Molecular and Cellular Biology of Cancer

MEDG 530 Human Genetics

MEDG 545 Current Topics in Medical Genetics Research

MEDG 548 Directed Studies

AWARDS

International Society of Experimental Hematology Travel Award

American Society of Hematology Travel Award

UBC Medical Genetics Entrance Scholarship

Instructors

Drs. A. Brooks-Wilson, M. Lorincz, R. McMaster, F. Rossi, C. Ross, W. Wasserman and E. Simpson

Drs. S. Dunn, M. Kobor, P. Lansdorp, A. Weng, C. Roskelly, M. Marra, A. Karsan and R. Kay
Drs. L. Clarke, W. Robinson, and L. Conibear
Drs. P. Hoodless and R. Kay
Dr. Xiaoyan Jiang

2008

2007

2006-2007

SELECTED PRESENTATIONS

Kennah, E., Ringrose, A., Qian, H., and Jiang, X. Identification of Differentially Expressed Genes in *AHL-1*-Mediated Leukemic Transformation of Human Cutaneous T-cell Lymphoma Cells by Microarray Analysis. 37th International Society of Experimental Hematology Meeting, American Society of Hematology, Boston, MA, July 9-12, 2008.

Kennah, E., Ringrose, A., Qian, H., and Jiang, X. Microarray Identification of Differentially Expressed Genes in *AHL-1*-Mediated Leukemic Transformation of Human Cutaneous T-cell Lymphoma Cells. 49th Annual Meeting and Exposition, American Society of Hematology, Atlanta, GA, December 8-11, 2007.