Reviewer's report

Title: Concomitant heterochromatinisation and down-regulation of gene expression unveils epigenetic silencing of RELB in an aggressive subset of chronic lymphocytic leukemia in males

Version: 2 Date: 4 January 2010

Reviewer: Erin Hertlein

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Major Compulsory Revisions

1. It would be beneficial to verify that RELB and other identified differentially expressed genes are similarly deregulated in male and female patient cells both sensitive and resistant to fludarabine treatment. While the authors reference a previous report that the gene expression following fludarabine treatment is comparable to that of ionizing radiation, as a major point of these findings is that the gene panel could potentially be used to predict response to treatment, wouldn’t it be important to verify this using a clinically relevant therapy?

2. The significance of RELB silencing in resistant males should be determined thru the analysis of any NF-kB target genes relevant to apoptosis or cell survival. Does the specific silencing of RELB result in differential regulation of NF-kB target genes?

Minor Essential Revisions

1. Figures 1B, C, D and E, Figure 2, and Figures 4A and B need better labels on the Y-axis describing the unit of measurement

2. Figures 4A and B, should “RH” and “SH” on the figure labels be “RM and “SM”?

3. For consistency, the actual P-value, rather than asterisks should be included on all figures

Discretionary Revisions

1. The effect of RELB silencing on the response to other CLL treatment options would be interesting. Is the expression of RELB required for response to some treatments but not others, such as antibody therapies such as rituximab or alemtuzumab?

2. It would be interesting to see if the re-expression or over-expression of RELB in the resistant samples sensitized them to cell death.

3. Unless otherwise omitted for space requirements, Supplemental Table 1 or an abbreviated table containing patient characteristics and apoptosis response could be included in main body of the paper