Reviewer's report

Title: Circulating levels of cell adhesion molecule L1 as a prognostic marker in gastrointestinal stromal tumor patients

Version: 1 Date: 16 November 2010

Reviewer: Deni Galileo

Reviewer's report:

Major Compulsory Revisions

None.

Minor Essential Revisions

1) For Figure 1, several things should be noted either in the text or figure legend. One is that UJ127 binds to a membrane proximal Fn repeat, which allows detection of both the ADAM-cleaved 180 kDa shed fragment and the 80 kDa membrane-bound fragment presumably generated by plasmin cleavage. GIST882 cells used in the study are not referenced or described, but need to be. The label “soluble L1” is between the full-length L1 and shed ectodomain fragments and, thus, is confusing to know to which arrows it refers. It appears that they are labeling both sets of bands as soluble L1, which cannot be. It is stated correctly that the 200-220 kDa bands represent full-length (membrane-bound) L1, but this weight of L1 shows up in the patient serum sample. The higher weight doublet band in the serum sample is clearly too heavy to be shed L1. The presence of full-length L1 in the serum sample needs to be pointed out in the Results and explained, even if by conjecture in the Discussion.

2) For Figure 2, several things on the graph are not explained. Not defined are 1) what the boxes represent, 2) the circles, 3) the asterisks, and 4) why the GIST box is gray.

3) For Figure 3, justification needs to be given for why 2 ng/ml was used as the critical value for high vs. low soluble L1. It would be useful to show on this plot the survival curves for the median values shown in Figure 2 or the mean values.

4) Although values are given in the text, serum L1 values also should be presented in another table for overall GIST patients vs. healthy controls. Better yet, it could be added to Table 1 at the top so that the overall values could be compared easily to the categories already presented there. It would also be useful to see values of each characteristic compared to healthy controls because it is not clear whether a specific characteristic has significantly higher L1 levels than controls. For instance, the highest mean serum L1 levels were from patients with the smallest tumors (< 2 cm) and it should be determined if this is significantly different as a group from controls. Additionally, there seems to be an inverse correlation between tumor size and serum L1 levels, so significance of
this also should be explored. The p-value of 0.305 is taken to mean that there is no significant difference in L1 levels between tumors of different size, but it appears that the most significant difference would be between healthy controls and the patients with the smallest tumors. It should be determined whether or not this is the case.

5) There is no discussion that the mechanism responsible for high serum L1 levels, namely L1 shedding, likely would also be responsible for a high degree of cell dispersal. This is implied but the 3rd paragraph of the Discussion should state the likely mechanistic tie between their finding of high serum L1 level, recurrence, and stimulation of cancer cell motility by soluble L1, since this is a well-known mechanism. The L1-mediated mechanism in GIST cells is highly likely to be another example of the general phenomenon of soluble L1-mediated autocrine stimulation of cancer cells.

Discretionary Revisions

1) A characteristic that could be more fully explored is recurrence. For instance, from Table 1 it could be hypothesized that since the smallest tumors led to the highest serum L1 levels, those tumors were the “smallest” because the cells were the most widely dispersed, which then led to the highest levels of recurrence. So, was there a significant correlation between recurrence and smallest tumor size? If this hypothesis was correct, then it would argue that patients with the smallest tumors should be treated most aggressively with systemic therapy because cells have likely dispersed by an L1-mediated mechanism. This paper does not really tie any data to L1-mediated cell dispersal mechanisms, but this is an example where maybe it could be done.

2) Limitations are not really discussed and should be briefly mentioned, if there are any.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests.