Reviewer's report

Title: Insulin-like growth factor I activates apoptotic pathways in colorectal cancer cells

Version: 2 Date: 5 November 2008

Reviewer: Jack Youngren

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Overview:

The authors present data suggesting that IGF-1 has pro-apoptotic effects in HT-29 colon cancer cells, with some corroboration in experiments with a couple other cell lines. They demonstrate a blockade of these effects by IGF-1R blockade employing specific receptor antibodies. These results are in direct contrast to published reports employing the exact same cell lines. The authors make mention of some of these contradictory studies in their introduction, referring to the "controversial" nature of the field. However, the authors do not take steps in their studies to ensure their validity in the face of contradictory reports.

Major Compulsory Revisions:

1. The authors must include other measures of apoptosis. While Caspase activation is a hallmark of apoptosis, only one type of assay is employed in these studies and the sole readout is luminescence with no way to assess the units. It is clear that the units employed to quantify caspase activity are relative and are highly different from graph to graph, which does not allow for a true understanding of the conditions of the cells. Preferrable would be a measure of the percentage of apoptotic cells. While this might be overkill in another paper, the authors are operating at the disadvantage that previous authors have shown that small molecule inhibitors of the IGF-1R (Piao et al Molecular Cancer Therapeutics, 2008) and monoclonal antibodies against the IGF-1R (Zhang and Zhang, Cancer Investigation, 2008) both induce apoptosis in these same cell lines.

2. To draw conclusions based on the use of downstream inhibitors, the authors should study the effects of IGF-1 incubation as well as the antibodies and kinase inhibitors on signaling through the respective pathways. If the reader is to believe that Akt is pro-apoptotic in these cells, a signaling scheme linking IGF-1 stimulation to pro-apoptotic pathways in the cell should be demonstrated.

3. The discussion should be expanded to discuss the directly contradictory studies and to offer possible explanations for the discrepant results. A discussion of the limitations of their study must be included. Any suggestion that IGF-1 derivatives might make ideal anti-cancer agents should be tempered by a thorough discussion of the body of work demonstrating the negative aspects of
IGF-1 on colorectal cancers.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I am an author on several patents for small molecule inhibitors of the insulin-like growth factor-1 receptor as treatments for a variety of cancer types. These compounds are not used in this work.