Reviewer's report

**Title:** Null Mutation for Macrophage Migration Inhibitory Factor (MIF) Is Associated with Less Aggressive Bladder Cancer in Mice

**Version:** 3 Date: 27 June 2007

**Reviewer:** Hiro-omi Kanayama

**Reviewer's report:**

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**General**

This manuscript showed for the first time the impact of MIF gene deletion on the development and progression of bladder cancer and demonstrated that MIF KO mice developed consistently lower stage tumors with less associated angiogenesis in a BBN model of bladder cancer. Generally this manuscript is well written and acceptable

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**Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)**

1) In this study, treated with BBN, muscle invasion was present in all MIF WT bladders, whereas MIF KO bladders had lower tumor stage with no invasion into muscle layers. In terms of cell growth, apoptosis, or angiogenesis, how do the authors speculate why the absence of MIF do not impair tumor development but is associated with the absence of tumor invasion especially into muscle.

2) As the authors mentioned, the role of MIF in cell proliferation, angiogenesis, or tumorigenesis remains unclear and seems very interesting. Do the authors have any data about the influence of MIF deficiency on MAPK, ERK, or PI3K pathways?

3) When you think about cell proliferation, Cyclin D1 for instance is a critical regulator involved cell cycle progression which controls cell proliferation, and did the authors study the expression or something of this factor under MIF influence?
4) In future, how are the authors planning to determine the role of MIF in human bladder cancer? How about the possibility of MIF as a specific marker for invasive bladder cancer?

5) There are some omitted characters to be corrected.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

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Discretionary Revisions (which the author can choose to ignore)

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**What next?**: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**Level of interest**: An article of importance in its field

**Quality of written English**: Needs some language corrections before being published

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