Reviewer's report

Title: Plasma MMP2 in combination with MMP9 and TIMP1 improves the non-invasive detection of transitional cell carcinoma of the bladder

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Reviewer: Cornelis Sier

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General

As the authors indicate, studies concerning the expression of MMPs in bladder TCC are relatively rare. Nevertheless, there is substantial evidence to expect that certain MMP levels in plasma could reflect the state of the tumour and therefore might have clinical relevance. In this study some members of the MMP cascade were measured in plasma of controls and bladder TCC patients. Despite a narrow range and substantial overlap, the data showed indeed significant differences between controls and patients. Next, within the patients the data were examined for correlations of MMPs with each other, and with tumour stage and grade. The most relevant correlation was found between MMP-9 and TIMP-1. From all the parameters, MMP-2 had the best diagnostic validity, highly significant according to ROC analysis. However, the relevance of MMP-2 as a single diagnostic tool is limited, as indicated by figure 3 (my request). Therefore, the diagnostic performance of combined markers was evaluated using relatively simple ratio- and a sophisticated computer program. The combination of MMP-2/MMP-9/TIMP-1 was found to possess highly significant diagnostic power, according to ROC statistics and visualized by figure 3c. Figure 3b shows clearly however, that the performance of the MMP-9/TIMP-1 combination is very similar to the combination of 3, and in fact much better than the best single parameter MMP-2. These rather interesting data are discussed as follows:

60 lines about MMPs in bladder tissue (reason of the study?).
13 lines about MMPs in serum (relevance?).
15 lines why plasma should be used in stead of serum (good point for introduction?).
30 lines of basically repetition of the results including:
One remark about TIMP-1, being enhanced in metastasized tumours, possibly being the result of the dual function as, discussed (=mentioned) before
One remark about the correlation between MMP-9 and TIMP-1 which could result in overfitting.
13 lines concluding that combination of indicators could improve sensitivity and specificity in comparison to single indicators.

In my opinion this discussion would only have been acceptable if the parameters were completely unrelated. But in the case of MMPs, it does not support the relevance of the data at all. Members of the MMP proteolytic cascade interact highly, and correlations can actually mean something with respect to proteolytic activity. The authors have published enough about the subject to explain why they think that some of these parameters are positively/negatively correlated, why some are high in metastasized tumours (derived from metastasis?), what the expected status of their parameters is (free, complexed, active), etc., etc. and what the consequences are for a possible diagnostic role. The data give enough possibilities to speculate, especially the MMP-9/TIMP-1 combination, and could give a biological reason/validation for making specific combinations for clinical purposes.

With respect to the validation of making combinations of different MMP parameters for diagnostic purposes, I would like to draw the attention on a recent review of Overall et al., where they point out in a very simple interaction scheme that the connections between the components in a biological system are more important than the single components.

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

The title is inadequate. The basic statement plasma MMP-2 improves the non invasive detection of cancer is simply not correct.
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Spelling errors
pg. 10; manufacture™s
guidelines. Using (no capital, comma?)
pg. 11; ROC analyzes (plural) were
g. 25; KJ-(he)
Table I; check ranges of MMP1 for controls and mBCa (identical?)
Table III; P-values apply also for 4th column
Table IV; missing â€œand- between TIMs and MMP1/TIMP1 complex in title
Table IV; use either MMP9xTIMP1 or MMP9+TIMP1 (see Figure 3)
Table IV; MMP9xTIMP1 -1.004 does not correspond with Figure 3, -0.996?)
Legend Figure 2; combination of MMP2 (!), TIMP1, and MMP9
Figure 3; please use closed and open dots for black/white reproductions

Discretionary Revisions (which the author can choose to ignore)

What next?: Accept after minor essential 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