Author's response to reviews

Title: Combined determination of plasma MMP2, MMP9, and TIMP1 improves the non-invasive detection of transitional cell carcinoma of the bladder

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Author's response to reviews: see over
Berlin, June 28th 2006

RE: Resubmission of original work manuscript:
No. 1736728878568775

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

New Title:
Combined determination of plasma MMP2, MMP9, and TIMP1 improves the non-invasive detection of transitional cell carcinoma of the bladder

Andrea Staack, Steffen Badendieck, Dietmar Schnorr, Stefan A. Loening, Klaus Jung
From the Department of Urology, University Hospital Charité, Humboldt University of Berlin, Germany

Dear Members of the Editorial Board,
Dear Dr. Sier,

We appreciated the valuable comments by Dr. Siers. We revised this manuscript with focus on the discussion in regards to his advice and provided a new title. In the Letter to the Editor we pointed out the changes, which have been made in the text.

We hope to have met the criteria this time!

Sincerely,

Dr. med. Andrea Staack
Reviewer’s report: Dr. Cornelis Sier

- **General**

The reviewer requests additional points in the Discussion to support the relevance of the data. He suggests discussing also the impact of interactions between components in a biological system as recently pointed out in the review by Overall et al.

We added the remark on the impact of interactions between components in a biological system in the Discussion at page 19, line 13 – page 20, line 9 as suggested by Dr. Sier.

We believe that the term “protease web”, introduced by Overall and Kleifeld, is useful to explain the complexity of processes taking place and the occurrence of the various components in tissue. However, that opinion has a limited value to attribute the circulating concentrations of MMPs and TIMPs to their tissue expression. Therefore, we have discussed that aspect using the well-known phenomenon of "enzyme distortion".

Dr. Sier asked about the status of the parameters (free, complexed, active). We stated that non-active parameters were measured using the ELISA technique in the Method section, page 10, line 8-10 and discussed that issue on page 20, lines 6-9.

- **Major compulsory revisions**

The title seems inadequate to the reviewer.

We changed the title to:

„Combined determination of plasma MMP2, MMP9, and TIMP1 improves the non-invasive detection of transitional cell carcinoma of the bladder“

- **The reviewer listed minor essential revisions.**

1. Spelling errors

We have changed the errors in the text according to the suggestions:

<table>
<thead>
<tr>
<th>Pg. 10; manufacture’s</th>
<th>Changed to: manufactures</th>
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<table>
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<tr>
<th>Pg. 10; Using</th>
<th>Changed to: The cubic-spline method was used for calculation of concentrations</th>
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<tr>
<th>Pg. 11; ROC analyzes</th>
<th>Changed to: ROC analyzes were performed</th>
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</table>
Pg. 25; KJ- (he) has

Changed to: KJ-has been

Table I; check ranges of MMP1 for controls and mBCa (identical)?

We confirmed the ranges in table 1; they are indeed identical for the controls and the group of patients with mBCa.

Table III; P-values apply also for the 4th column

Apparently, the labeling in row 1 was not distinct. The p-values also apply for column 4. Therefore, we shifted the labeling to the middle, though the reader can apply it to column 3 and 4 more easily.

Table IV- missing an “and” between TIMPs and MMP1/TIMP1-complex

We added “and” in the title of Table IV.

Table IV- use either MMP9xTIMP1 or MMP9+TIMP1

We decided to use “+” and therefore made the appropriate changes in Table IV.

Table IV- MMP9xTIMP1-1.004 does not correspond with Figure 3 –0.996?

Apparently, Dr. Siers might have mistaken the charts B and C in figure 3. Our data confirm the numbers in the charts. The value for the combination of MMP9+TIMP1 is −1.004 and for MMP2+TIMP1+MMP9 is 0.745, which is shown in figure 3 and also presented in table IV.

Legend Figure 2; combination of MMP2 (!), TIMP1, and MMP9

We have made the change in the text.

Figure 3; please use closed and open dots for black/white reproductions

We made the requested changes in figure 3.