Author's response to reviews

Title: Corticosteroid co-treatment induces resistance to chemotherapy in surgical resections, xenografts, and established cell lines of pancreatic cancer

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Version: 2 Date: 22 December 2005

Author's response to reviews: see over
Submi ssion of the revised Manuscript 8566779128318383 by Zhang et al.

Dear Editors,

Please find enclosed a revised version of our manuscript, a marked manuscript, a marked manuscript currently submitted to Clinical Cancer Research, and a point-by-point response to the comments of the Editor and reviewers. We hope, that our manuscript will be now acceptable for publication in BMC CANCER.

Thanking you in advance for your time and effort.

Ingrid Herr
Point-by-Point Response

Suggestions of the medical Editor of BMC Cancer:
1. While we are ready to proceed with the peer review process of the current submission to BMC Cancer, we would urge you clearly state on the manuscript under consideration by Clinical Cancer Research that a good part of the data and information are overviews or further analysis of results published or under consideration elsewhere.

Our response and changes: Yes, we agree. As suggested by Dr. Kofler, who was the reviewer of the former PLOS Medicine manuscript, we already made the appropriate changes in the revised manuscript which is now under consideration by Clinical Cancer Research. This paper contains now the required information and cross-references regarding the point that our published or submitted data are combined in tables. Please compare the marked manuscript submitted to Clinical Cancer Research.

2. As requested by Reviewer 1 (please see below), and in the light of the separate submission to Clinical Cancer Research, we would also urge you to tone down any claims regarding the novelty of the data presented in this submission under consideration by BMC Cancer.

Our response and changes: Yes, we agree, any claims regarding the novelty of the data presented in the present BMC Cancer submission are toned down – please compare the marked manuscript.

Referee 1, Reinhard Kofler:

General
Zhang et al. address the clinically important issue of whether GC co-medication in pancreatic cancer treatment might affect the efficacy of cytotoxic drugs and conclude that GC induces therapy resistance in pancreatic carcinoma cells. This is an important issue, the work is well done and clearly presented.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached). There is, however, a major problem that needs to be resolved between the authors and the editors. The majority of the data has simultaneously been submitted elsewhere. More specifically, I received the invitation to review this manuscript while I was reviewing another manuscript by the same group (same first and last author) submitted to PLoS. Figures 1, 2, 4 and 5 of the BMC manuscript are identical to the ones contained in the supplement to the PLoS manuscript. Figure 6 of the BMC paper corresponds to the lower left panel of Figure 1a of the PLoS manuscript, and 4 of the 5 supplementary tables in the BMC manuscript are identical to the corresponding pages in the supplement to the PLoS paper. The Western analyses in Figure 7 are new and add some information related to our understanding of the protective GC effect. The PLoS paper deals with GC-induced resistance in many different solid tumors including pancreatic tumors. Since the paper is very complex, it might indeed be useful to discuss and extend (e.g., by Western analysis) the data related to pancreatic cancer in a separate publication. However, the 2 papers should be cross-referenced and sentences like “These data show for the first time that DEX induces therapy resistance in pancreatic carcinoma cells ...” (Abstract, Conclusion) should better be omitted to avoid confusion. I suggest that the authors contact the editors of the 2 Journals to find out how to best deal with this issue.

Our response and changes: Yes, we agree. Since we received the review of Dr. Kofler for the former PLOS Medicine manuscript prior to the present review, we already made the appropriate
changes in the revised version currently submitted to Clinical Cancer Research. Please compare our answer to the comments of the Editor and the attached and marked Clinical Cancer Research Manuscript.

Referee 2, Margaret Briehl:

General:
In this study, the authors address the question of whether dexamethasone (DEX) impacts the sensitivity of pancreatic cancer cells to gemcitabine or cisplatin. This is an important question because DEX is used in combination with these agents to prevent undesirable treatment side effects. The study provides the first evidence that DEX could actually be reducing the efficacy of treatment for pancreatic cancer. The evidence appears strong, since the experiments were conducted with 10 different pancreatic cancer cell lines, primary cultures of 20 pancreatic cancer specimens and xenografts of one pancreatic cell line. The conclusion that DEX induces therapy resistance in pancreatic carcinoma cells is supported by the data, particularly the results seen with primary tumor specimens and xenografts.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
1. The title should be revised to better convey the major finding from the study.
Our response and changes: Yes, we agree and revised the title – please compare the attached marked manuscript.

2. The inability to detect a correlation between induction of therapy resistance and patient age, gender, histology or TMN may be due to the sample size. Was a power analysis conducted to determine how many samples would need to be analyzed to detect a correlation?
Our response and changes: Since we made similar observations using tumour samples derived from ovarian, prostate, colon, rectum and lung cancer we did not perform a power analysis. This point is discussed – please compare marked manuscript.

3. The Methods section should include the source of the cell lines.
Our response and changes: Yes, we agree and included the required information – please compare the attached marked manuscript.

4. The statistical analyses description in the Methods section is difficult to follow. Was the value of 0 or 1 assigned depending on whether or not the DEX dose group was declared resistant? Is there a maximum score of 9 per time point because the effect of DEX alone (Drug 0 row in the example scheme) not included in the score? If yes, why is this row included in the sum column? What do the numbers in the 'Treatments' column signify?
Our response and changes: Yes, we agree and revised the description of statistical analysis to make it better understandable for the reader. To further clarify this issue, we added a line in the table to distinguish the maximum score of the "9 block" from the "drug 0 row". Please compare the attached marked manuscript.

5. The Results section (1st paragraph) states that 'the presence of DEX neutralized the cytotoxic effect in all cell lines (Fig 1B, 2B).' Based on this statement, one expects that the viability in the combined treatments would be the same as in the control. This is not the case for the majority of the cell lines. Indeed, the variation in the experiments makes it questionable whether the results with the combined treatments are statistically different than with the cytotoxic drug alone for
many of the cell lines.

*Our response and changes:* Yes, we agree. We replaced the term "neutralized" by the term "diminished" to better reflect the situation. Please compare marked manuscript.

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

*Our response and changes:* Yes, we agree. A native English speaker made the appropriate changes.