

Format for ANSWERING REVIEWERS

August 6, 2015

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 20026-Review.doc).

Title: Inorganic phosphate in the development and treatment of cancer: A Janus Bifrons?

Author: Sapio Luigi, Naviglio Silvio

Name of Journal: *World Journal of Clinical Oncology*

ESPS Manuscript NO: 20026

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

REPLY TO COMMENTS FROM REVIEWERS: 02992710, 02537632, 02676022.

Thank you very much for your kind comments.

REPLY TO COMMENTS FROM REVIEWER: 02680711

Thank you very much for your criticisms and suggestions.

The possibility that Pi could sensitize normal cells to doxorubicin and thereby enhance toxicity to cells such as cardiomyocytes is a very important point; It will be further addressed in future studies.

In the meantime, please kindly note that the enhancement of doxorubicin-induced cytotoxicity is not a Pi-induced widespread phenomenon; I mean, we have evidence that Pi does not enhance doxorubicin-induced cytotoxicity in osteosarcoma Saos and MG63 cells, breast cancer MCF-7 cells (to make some examples). We don't know about Pi/doxo effects on cardiomyocytes. This is a very good suggestion, since it is largely known that doxorubicin causes an important cardiotoxicity.

However, it's important to keep in mind that by our findings it is absolutely not suggested that it should be increased Pi concentration at systemic level to treat cancer, but just that up-regulating Pi levels at local sites (such as bone and not heart!) for brief times, might contribute to the development of novel and cheap modalities for therapeutic intervention in some tumors.

Overall, we do know that the influence of Pi on cell function and the possible relationship to cancer have to be fully understood and investigated further.

3 References and typesetting were corrected

As required, we have completed the revision process according your indications.

Thank you very much for your kind attention and assistance.

We hope that the revised Manuscript will definitively meet the criteria for publication in World Journal of Clinical Oncology.

Best regards,

Silvio Naviglio MD, PhD

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