Name of journal: World Journal of Gastrointestinal Oncology

Response letter Manuscript NO 15877

Reviewer 1 request: the figures are adopted from published manuscripts, the copy right transfer should be obtained.

Our response: We appreciate the reviewer calling attention to other places in which the 4 figures in our paper also appeared. All of them allow re-use of the figures. We have amplified our references to these other occurrences of these figures in our current editorial review article.

Figure 1 has appeared as a Wikimedia file, licensed under a Creative Commons license, and is free for re-use as long as the Wikimedia file is referred to and this reference was previously made within reference 45. A portion of this figure also appeared in a previously published article in World Journal of Gastrointestinal Oncology which allows re-use under Copyright ©1995-2014 Baishideng Publishing Group Inc. All rights reserved. Articles published by this open-access journal are distributed under the terms of the Creative Commons Attribution-Noncommercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license. Both previous Figures are now referred to in the reference to Figure 1, reference 45, which has been amplified as follows:

45 This image appears in http://commons.wikimedia.org/wiki/File: Image_of_resected_colon_segment_with_cancer_%26_4_nearby_polyps_plus_schematic_of_field_defects_with_sub-clones.jpg This file is licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license. This image is free for re-use as long as the Wikimedia file is referred to. The top portion of this figure also appears in Prasad AR, Prasad S, Nguyen H, Facista A, Lewis C, Zaitlin B, Bernstein H, Bernstein C. Novel diet-related mouse model of colon cancer parallels human colon cancer. World J Gastrointest Oncol. 2014 Jul 15;6(7):225-43. doi: 10.4251/wjgo.v6.i7.225. PMID: 25024814 This article is Copyright ©1995-2014 Baishideng Publishing Group Inc. All rights reserved. Articles published by this open-access journal are distributed under the terms of the Creative Commons Attribution-Noncommercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

Figure 2 has appeared as a Wikimedia file, licensed under a Creative Commons license, and is free for re-use as long as the Wikimedia file is referred to and this reference was previously made within reference 47. A modified form of this figure also appeared in a previously published article in World Journal of Gastrointestinal Oncology which allows re-use under Copyright ©1995-2014 Baishideng Publishing Group Inc. All rights reserved. Articles published by this open-access journal are distributed under the terms of the Creative Commons Attribution-Noncommercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license. Both previous Figures are now referred to in the reference to Figure 2, reference 47, which has been amplified as follows:

47 This image has previously appeared in http://commons.wikimedia.org/wiki/File: Expression_of_DNA_repair_proteins_ERCC1,_PMS2_%26_KU86_in_field_defect.jpg This file is licensed under a Creative Commons license, and is free for re-use as long as the Wikimedia file is referred to. A modified form of this figure also appeared in Bernstein C, Nfonsam V, Prasad AR, Bernstein H. Epigenetic field defects in progression to cancer. World J Gastrointest Oncol. 2013 Mar 15;5(3):43-9. doi: 10.4251/wjgo.v5.i3.43. PMID:23671730 . This article is Copyright ©1995-2014 Baishideng Publishing Group Inc. All rights reserved. Articles published by this open-access journal are distributed under the terms of the Creative Commons Attribution-Noncommercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

Figure 3 has appeared in a Wikimedia file, but was adapted to only include DNA repair genes epigenetically modified in gastrointestinal cancers. This file is licensed under a Creative Commons license, and is free for re-use as long as the Wikimedia file is referred to. The reference to this Wikimedia was previously omitted, and this has now been rectified by including a reference to the Wikimedia file within Figure 3. The reference is now reference 78, and references subsequent to reference 78 have been renumbered to accommodate this new reference. Figure 3, reference 78, has been inserted as follows:

78 This figure was adapted from a Wikimedia image and only includes DNA repair genes epigenetically modified in one or more gastrointestinal cancers: http://commons.wikimedia.org/wiki/File:DNA_damage,_repair,_epigenetic_alteration_of_repair_in_cancer.jpg This file is licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license. This image is free for re-use as long as the Wikimedia file is referred to.

Figure 4 has appeared as a Wikimedia file, licensed under a Creative Commons license, and is free for re-use as long as the Wikimedia file is referred to. A modified form of this figure also appeared in a publication under the Creative Commons license as well, which permits unrestricted use as long as the original work is properly cited. A still more modified form of this figure appeared in a previously published article in World Journal of Gastrointestinal Oncology which allows re-use under Copyright ©1995-2014 Baishideng Publishing Group Inc. All rights reserved. Articles published by this open-access journal are distributed under the terms of the Creative Commons Attribution-Noncommercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license. All three Figures are now referred to in the reference to Figure 4, reference 79, which has been amplified as follows:

79 http://commons.wikimedia.org/wiki/File: http://commons.wikimedia.org/wiki/File:Diagram_Damage_to_Cancer_Wiki_300dpi. svg This file is licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license. This image is free for re-use as long as the Wikimedia file is referred to. The figure was adapted from Bernstein C, Prasad AR, Nfonsam V, Bernstein H. (2013). DNA Damage, DNA Repair and Cancer, New Research Directions in DNA Repair, Prof. Clark Chen (Ed.), ISBN: 978-953-51-1114-6, InTech, http://www.intechopen.com/books/new-research-directions-in-dna-repair/dna-damage-dna-repair-and-cancer . c 2013 Bernstein et al.; licensee InTech. This is an open access

Reviewer 2, two requests:
Request 1 of reviewer 2: The manuscript is too long.

Our response: We removed a number of sections of text that were not central to the manuscript. These are indicated below and shown in the revised manuscript as crossed-out and highlighted text segments.

We removed unnecessary details of translesion synthesis shown here:

REV1 inserts cytosine opposite abasic sites in DNA (which may not be the correct base for that site) and has a structural role in regulating Pol ζ. Pol ζ extends replication past distorted DNA pairs, such as mismatched pairs of bases or bases with bulky DNA adducts. Pol η is a DNA polymerase that efficiently replicates DNA templates containing thymine dimers. Pol ι utilizes Hoogsteen base pairing for efficient and correct incorporation of cytosine opposite altered purines, such as 8-oxoguanine, but also tends to incorrectly incorporate guanine opposite thymine. Pol κ is specialized in performing error-free bypass of bulky minor groove N2-deoxyguanine adducts among other lesions, but is highly error-prone when replicating a normal portion of a template.

We removed unnecessary details of DNA repair shown here:

This included proteins SIRT1, EZH2, DNMT1, and DNMT3B. In addition, silencing histone modifications occurred including hypoacetyl H4K16, H3K9me2 and me3, and H3K27me3.

We removed unnecessary details of another DNA repair system shown here:

The meganuclease I-SceI, which does not otherwise cleave the eukaryotic genome, creates a unique DSB. The DSB is repeatedly formed and repaired, until the *I-SceI* site is lost by homologous or nonhomologous repair or by depletion of the I-SceI enzyme. Recombination products can be detected by direct analysis of the DNA flanking the DSB or by the appearance of functional GFP (green fluorescent cells).

We removed an unnecessary description of a colonic crypt shown here:

A colon resection, on its inner epithelial surface, has a layer of microscopic epithelial crypts (test tube- like indentations about 100 cells deep and about 50 cells in circumference), with 100 crypts per square millimeter. Each crypt is a clone of about 5,000 cells all generated by the roughly 10 stem cells at the base of the crypt.

We removed an unnecessary description of the mechanism of action of the HMGA2 protein shown here:

HMGA proteins are characterized by three DNA-binding domains, called AT-hooks, and an acidic carboxy-terminal tail. HMGA proteins are chromatin architectural transcription factors that both positively and negatively regulate the transcription of a variety of genes. They do not display direct transcriptional activation capacity, but regulate gene expression by changing local DNA conformation.

We removed some wording that repeats material shown in figure 3 as shown here:

The major DNA repair pathways are base excision repair, nucleotide excision repair, homologous recombinational repair, non-homologous end joining, mismatch repair and direct reversal. Each of these repair pathways employs one or more DNA repair enzymes that are frequently epigenetically reduced in expression in one or more types of GI cancer.

We removed some wording that may have been redundant is describing synthetic lethality, as shown here:

Synthetic lethality refers to the requirement that two DNA repair defects (one present naturally in the tumor and one exogenously introduced) be present for cell death to occur, especially upon chemotherapy with a DNA damaging agent. When an agent damages DNA in a tumor cell, its effects on the cell can be amplified if the efforts of the cell to repair the damage are inhibited even more, by exogenous interference with an additional DNA repair pathway.

Request 2 of reviewer 2: The authors should to recommend the readers to apply this knowledge into the routine clinical practice.

We have added text, near the end of the manuscript, as follows:

When Phase III trials indicate which efforts at synthetic lethality are beneficial therapeutically, synthetically lethal down regulation of DNA repair pathways should be incorporated into standard medical treatments of cancers.

Editor's request: A conflict-of-interest statement is required for all article and study types. In the interests of transparency and helping reviewers to assess any potential bias in a study's design, interpretation of it results or presentation of its scientific/medical content, the BPG requires all authors of each paper to declare any conflicting interests (including but not limited to commercial, personal, political, intellectual, or religious interests) in the title page that are related to the work submitted for consideration of publication. In addition, reviewers are required to

indicate any potential conflicting interests they might have related to any particular paper they are asked to review, and a copy of signed statement should be provided to the BPG in PDF format.

Our response: We have added the sentences to our title page :
Carol Bernstein has no conflicts of interest.

Harris Bernstein has no conflicts of interest.

Editor's request: Please add PubMed citation numbers and DOI citation to the reference list and list all authors. Pleased provide PubMed citation numbers for the reference list, e.g. PMID and DOI, which can be found at http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed and http://www.crossref.org/SimpleTextQuery/, respectively. The numbers will be used in the E-version of this journal. Thanks very much for your co-operation.
Such as: 1 **Nayak S**, Rath S, Kar BR. Mucous membrane graft for cicatricial ectropion in lamellar ichthyosis: an approach revisited. *Ophthal Plast Reconstr Surg* 2011: e155-e156 [PMID: 21346670 DOI: 10.1097/IOP.0b013e3182082f4e]

Our response: We put all our references through http://www.crossref.org/SimpleTextQuery/ and then added all urls provided by this site to all our references. We are not sure that this is what was requested.

Editor's request: Figure 3 had the request: "Would you please provide the decomposable figure of Fiugres, whose parts are movable and words can be edited."

Our response: We have now replaced the previous Figure 3 with a decomposable Figure 3.

Editor's request: Figure 4 had the request: "Would you please provide the decomposable figure of Fiugres, whose parts are movable and words can be edited."

Our response: We have now replaced the previous Figure 4 with a decomposable Figure 4.