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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 42884

Title: Colorectal Cancer Vaccines: Tumor-associated antigens versus Neoantigens

Reviewer's code: 00291404

Reviewer's country: United States

Science editor: Xue-Jiao Wang

Date sent for review: 2018-10-18

Date reviewed: 2018-10-19

Review time: 1 Day

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[Y] Minor revision	[ ] Onymous
[ ] Grade D: Fair	[ ] Grade D: Rejection	[ ] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[Y] Advanced
			[ ] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

The authors have done a very decent review on most parts of the cancer vaccines for colorectal cancer, and provides some valid perspective on the future of the field. The authors have tried to cover most, if not all, approaches of cancer vaccines, including the use of immunogenic chemotherapies. However, it seems that one obvious was missed,

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which play more and more important roles in cancer therapy and cancer vaccine. Oncolytic viruses have been shown to induce immunogenic cell death and can induce tumor-specific CD8 and CD8+ T cell responses. Indeed, these oncolytic viruses may function as potent therapeutic vaccines. Thus, it may be appropriate to add a paragraph (on page 15?) and make a short discussion on this particular class of cancer vaccines. Articles for references may be, (1). Bartlett DL et al. Oncolytic viruses as therapeutic cancer vaccines. Mol Cancer. 2013; 12:103. (2). Russell SJ, Barber GN. Oncolytic Viruses as Antigen-Agnostic Cancer Vaccines. Cancer Cell, 2018; 33: 599-605. Minor issues. 1. It needs some minor improvements in English language and use of certain terminology. A few examples are as follows, (1). In Introduction: "One promising approach to further improve this type…" should be "one approach to further improving this type…".. (2). "Checkpoint inhibition" should be changed to "immune checkpoint inhibition", as they are a variety of checkpoints these days, such as metabolic checkpoint. 2. Page 14, line 11, and other places. "MSI+ CRC…" In literature, the most common way to describe the status of MRI is "MSI-high" and "MSI-low", not MSI+. 3. Page 16, line 8. MSS+ CRC. Is it a typo in "MSS+"?

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 42884

Title: Colorectal Cancer Vaccines: Tumor-associated antigens versus Neoantigens

Reviewer's code: 02446022

Reviewer's country: Italy

Science editor: Xue-Jiao Wang

Date sent for review: 2018-10-18

Date reviewed: 2018-10-31

Review time: 13 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[Y] Minor revision	[ ] Onymous
[ ] Grade D: Fair	[ ] Grade D: Rejection	[ ] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[ ] Advanced
			[Y] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

Authors address the topic of vaccination in the setting of colorectal cancer (CRC). This is a very interesting topic, especially in the context of the success that immunotherapy, namely the use of immune checkpoint inhibitors (CPI), is proving in different cancer indications, including the MSI+ CRC patients. Some inaccuracies are present, and need

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to be corrected. Additional general and specific suggestions are provided below. General comment: Authors are encouraged to critically evaluate the role that vaccination could have in the current era of CPI. In other words, to me the review does not communicate what the authors suggest/feel/imagine as a best setting for vaccination in order to improve immune eradication of CRC. Would it be best in cancers that lack/are deficient in antigen-specific T cells (improve priming and eliciting antitumor immune response)s? Hot/cold tumors, from an immunological point of view? Authors imagine a role of vaccination also in tumors with abundant presence of immunosuppressive cells/molecules, and with what rationale? Any different role imagined in MSI vs MSS tumors? Specific comments: 1) Abstract, „two general classes of target structures", could read, "….target molecules" or "…..targets." 2) Core tip, "an extremely promising novel tool", should read "…..promising tool". 3) Core tip, „…due to their unspecificity, they frequently trigger severe adverse events. This risk is neglectable …." This needs to be rephrased/toned down: the SAE reported by authors were triggered by the use of adoptively transferred peptide-specific T cells and not by vaccination. Inference is not possible. 4) Core tip, „Intelligent modern CRC vaccines will combine several or", should read "….will likely combine several or". 5) Introduction, „peptides alone or loaded onto antigen presenting cells". Why do author focus only on APC? 6) Authors should include a table summarizing: vaccination strategies, peptides used, adjuvants, number of enrolled patients, clinical results, sorted by antigen type (TAA vs tumor-specific), etc. 7) Carcinoembryonic antigen, "the efficiency of CEA peptide vaccines was overall not satisfying[7]." Numbers should be provided. 8) Melanoma associated antigen, "The melanoma associated antigen (MAGE),". Specify that MAGE are representative of a specific class of TAA the CTA. 9) Melanoma associated antigen, "A vaccination study with melanoma cell lysate", If melanoma cell lysate is used, it could not be defined as vaccination with MAGE antigens. 10) Melanoma

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associated antigen, "40 % of MAGE-positive CRC", which of the MAGE antigens? 11) Neoantigens – truly tumor-specific antigens, "neoantigens have only recently been accepted as ideal targets for successful immunotherapy", authors should mention their possible involvement in predicting response to CPI. 12) TGFβRII and other frameshift mutations, "…coding microsatellites: PTHL3, HT001, TGFβIIR, AC1, ACVR2,….", TGFβIIR is repeated from the section above. 13) TGFβRII and other frameshift mutations, "In addition MARCKS-1, MARCKS-2, TAF1B - 1, PCNXL2 - 2, TCF7L2 - 2, Baxα+1[47] as well as CREBBP, EP300, TTK[48] have been suggested to be taken into consideration for developing cancer vaccines for MSI+ CRCs." Authors should argument on why a specific focus for developing cancer vaccines has been put on these gens or rephrase. 14) TGFβRII and other frameshift mutations, "containing peptides of frameshifted AIM2,", AIM2 was not included in the list of genes reported in the previous part of the section as containing frameshift mutations. 15) Point mutations: KRAS, does CRC have point mutations that could provide neoepitopes only in KRAS? 16) Genetic Configuration and Target Selection, "This lowers the risk of SAEs by only enhancing the existing antitumoral immune response instead of creating new targets." So pursuing new targets is discouraged by the authors? For some scientists the higher the number of neoepitopes targeted, the higher the possibility to evade antigen-driven imune escape. 17) Single peptides, peptide-loaded antigen-presenting cells or ex vivo expanded T cells?, ". In addition, the patient's individual set of HLA alleles also influences the efficiency of a peptide vaccine.", authors need to explain. 18) Single peptides, peptide-loaded antigen-presenting cells or ex vivo expanded T cells?, "To evade HLA restriction, longer peptides (15-30-mer),.." and "Another way to circumvent HLA restriction as..", authors should better detail what they intend on "circumventing/evading HLA restriction", which effector cells are expected to do the job? 19) Adjuvants, authors should comment on pros and cons of the available adjuvants.

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Is there any one which would be preferable? 20) Adverse events, "In a study with engineered anti-CEA T cells, the.." and below, authors need to be careful not to lead the reader to infer SAE from vaccination with TAA stemming from SAE observed using adoptively transferred T cells. 21) Adverse events, "The treatment with autologous anti-MAGE-A3 engineered T cells…", recognized peptide is shared by MAGE-A3/A9/A12. 22) Cancer vaccines: The solution to immune evasion? An effort should be made to make clear how cancer vaccines are proposed to takle the immune evasion mechanisms reported, e.g. HLA loss. 23) Immune check point inhibitors, „, PD-L1, LAG-3, and IDO", to my knowledge, IDO is not generally considered an immune checkpoint. 24) Immune check point inhibitors, „In clinical trials, almost 80 % of MSI+ CRC patients benefitted from PD-1 blockade whereas microsatellite stable (MSS+) CRC patients rarely did[94,93].". Please provide range and type of responses observed in the different trials. Besides, would authors suggest a different expected impact of vaccination on survival of MSI vs MSS patients? 25) Immune check point inhibitors, „, but the correlation between infiltrating lymphocytes and overall survival is only in MSS+ patients significant[95,96]. ", is there conflicting literature evidence on this? 26) Conclusion, authors should consider providing a table with current number of trials evaluating peptide cancer vaccines, as monotherapy or in combination, sorted by TAA and tumor-specific ones to give the feeling of the current interest in the topic. 27) Conclusion, "These genetic alterations can..", not always associated to genetic alterations (e.g. epigenetic, regulatory?).

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 42884

Title: Colorectal Cancer Vaccines: Tumor-associated antigens versus Neoantigens

Reviewer's code: 03252972

Reviewer's country: China

Science editor: Xue-Jiao Wang

Date sent for review: 2018-10-26

Date reviewed: 2018-11-03

Review time: 7 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[Y] Minor revision	[ ] Onymous
[ ] Grade D: Fair	[ ] Grade D: Rejection	[ ] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[ ] Advanced
			[Y] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

The authors reviewed the literature with regard to the colorectal cancer vaccines. It is a very decent summary of the topic with very clear structure and good evidence. The topic is an important one nowadays with increasing clinical attention. To provide an overview of this topic, I would suggest to use several figures illustrating the mechanism of the

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vaccines and the targets mentioned in the manuscript.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 42884

Title: Colorectal Cancer Vaccines: Tumor-associated antigens versus Neoantigens

Reviewer's code: 00044333

Reviewer's country: South Korea

Science editor: Xue-Jiao Wang

Date sent for review: 2018-10-23

Date reviewed: 2018-11-07

Review time: 15 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[Y] Grade B: Very good	[ ] Grade B: Minor language polishing	[Y] Accept (General priority)	[Y] Anonymous
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[ ] Grade D: Fair	[ ] Grade D: Rejection	[ ] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
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			[ ] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

The authors presented a review of colorectal cancer vaccines, and the manuscript is well-organized and written well with detailed data. Some part like clinical trials is complicated to understand. So, if possible, summary with table of clinical trials or figures on concept of colorectal cancer vaccines could be helpful to improve the readers'

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understanding.

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