

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Transplantation

ESPS manuscript NO: 26566

Title: Biology of chronic graft-vs-host disease: Immune mechanisms and progress in biomarker discovery

Reviewer's code: 03289840

Reviewer's country: United States

Science editor: Shui Qiu

Date sent for review: 2016-04-19 09:57

Date reviewed: 2016-05-28 11:38

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input checked="" type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

This is a very well written review. I have no major comments.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Transplantation

ESPS manuscript NO: 26566

Title: Biology of chronic graft-vs-host disease: Immune mechanisms and progress in biomarker discovery

Reviewer's code: 00345029

Reviewer's country: Austria

Science editor: Shui Qiu

Date sent for review: 2016-04-19 09:57

Date reviewed: 2016-06-06 17:36

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

COMMENTS TO AUTHORS

The author performed a review on the pathobiology of chronic graft-versus-host disease. This is an important topic and of high interest for the stem cell transplant community. Major concerns: Chronic classic GVHD is not the same as de novo cGVHD since quiescent onset type of cGVHD can also be chronic classic GVHD when features of acute GVHD are missing at the onset of cGVHD. The description of skin manifestations in the text is misleading since no distinction between diagnostic, distinctive and common signs is made. Please use these NIH recommendations to avoid confusion of the readers. Repeatedly the presence of autoantibodies is described. However, Miklos et al. could also demonstrate alloantibodies in sexmismatched HSCT. The references on page 19 do not concern autoantibodies. In the section of Pathobiology important issues are missing: discussion of cellular findings in the peripheral blood versus in tissue specimens; data on lichenoid versus sclerodermatous skin manifestations; other changes in regulatory T cells; distortion of B cell homeostasis and changes in B cell subsets; B cell deficiency in bone marrow, increased BCR responsiveness; increased susceptibility to apoptosis of Treg and B cells; role of regulatory B cells. Please also add different cell

subsets in Table 2. In the Biomarker section the NIH 2014 consensus update should be mentioned since substantial changes were agreed on regarding biomarker assessment. Please discuss the impact of immunosuppressive treatment including steroids on soluble biomarkers e.g. BAFF and CXCL9. In the section on Autoantibodies important data on the association with scleroderma or distortion of B cell homeostasis is missing. Furthermore, cellular biomarkers should be included into the manuscript. Minor issues: Please provide a reference for the incidence of cGVHD on page 3! On page 4 important references on treatment strategies for cGVHD are missing. On page 6 second line reference 9 is not appropriate. Oral mucocoeles have been removed from the NIH 2014 consensus update since they are unspecific. On page 7 fourth line from the bottom the sentence needs correction in wording. On page 9 second line reference 9 is inappropriate. On page 13 immature B cells is not correct. The reference on page 14 concerns acute GVHD and not chronic GVHD. Furthermore, the Ruxolitinib mouse model is not mentioned. In Table 1 the references under 2 should be 10 and 12.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Transplantation

ESPS manuscript NO: 26566

Title: Biology of chronic graft-vs-host disease: Immune mechanisms and progress in biomarker discovery

Reviewer's code: 03633737

Reviewer's country: China

Science editor: Shui Qiu

Date sent for review: 2016-04-19 09:57

Date reviewed: 2016-06-03 08:38

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input checked="" type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Duplicate publication	
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input type="checkbox"/> Minor revision
	<input type="checkbox"/> Grade D: Rejected	BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

The manuscript by Presland aims to review the The Pathobiology of Chronic Graft-versus-Host Disease. I found the manuscript lacking in its current form. Major concerns: 1. The title of the manuscript is extremely broad, and should be more focused. 2. The part of "INTRODUCTION" is very long and tedious, Table1 and figure1 should not showed in "INTRODUCTION". Hence, The part of "INTRODUCTION" should be refined and concise 3. This manuscript is to review "The Pathobiology of Chronic Graft-versus-Host Disease". However, author described the parts of "Clinical features" and "Risk factors of chronic GVHD". I think the two parts are not required. 4. The parts of "Animal models of chronic GVHD" and "Chronic GVHD Biomarkers" are also far away from the title. Over assessment, the review should be rewritten and more focused.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Transplantation

ESPS manuscript NO: 26566

Title: Biology of chronic graft-vs-host disease: Immune mechanisms and progress in biomarker discovery

Reviewer's code: 03509461

Reviewer's country: Italy

Science editor: Shui Qiu

Date sent for review: 2016-04-19 09:57

Date reviewed: 2016-06-03 20:51

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Duplicate publication	
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Minor revision
	<input type="checkbox"/> Grade D: Rejected	BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

The manuscript by RB Presland deals with distinct aspects of the pathobiology of chronic GvHD: this complication represents an important issue, since its incidence is expected to grow in the next future and its therapeutic control is far to be optimal; thus, the pathobiology is of paramount importance in the attempt to improve the prognosis of patients and to conceive newer and more powerful therapeutic strategies. All the main topics are discussed here; however, some modification have to be made before the review is ready to be published, as follows: "Introduction" - Since the GvT effect is also applicable to diseases other than leukemia or NHL (i.e. myeloma or Hodgkin lymphoma), those terms must be replaced by "hematological malignancies" "Clinical features" section - It is uncorrect to state that classic cGvHD is like de novo one, indeed "classic" refers to the clinical characteristics, whereas "de novo" refers to the fact that cGvHD occurs without a previous acute GvHD. For this reason the concept of "classic" is opposed to "overlap" and the concept of "de novo" is opposed to both "progressive onset" and "quiescent", the latter ones referring to cGvHD occurring continuously after acute GvHD and after a previous acute GvHD that had undergone in

remission, respectively. Please avoid the confusion between “classic” and “de novo” in this and in the subsequent parts of the manuscript - The statement “Cellular epithelial apoptosis is a hallmark.....cytotoxic T-cells [17]” refers to anatomopathological features and not clinical ones, thus it has to be removed from this section “Risk factors of chronic GVHD” section - Please change “NRM within patients during the first 100 days post-transplantation” into “early NRM” “Regulatory T-cells” section - I do not agree with the statement that “...approaches that manipulate T-reg numbers or activity have had limited clinical utility to date”, because at least two recent papers (Peccatori J et al., Leukemia 2015 and Martelli MF et al., Blood 2014) argue in favor of some clinical benefit in manipulating T-regs. Please correct accordingly the sentence and add both references in the manuscript “B-cells” section - I would change “numerous clinical studies with Rituximab” into “numerous clinical observations with Rituximab”, since the evidence derive from reports and observations rather than from clinical trials “Serum biomarkers” section - Please refer (it may be suitable at the end of the section) to current research projects aiming at prospectively identifying and/or validating biomarkers, i.e. the “Cryostem project”, funded by the French National Research Agency “References” - Reference [20]: the year of publication is lacking (2010): please add it

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Transplantation

ESPS manuscript NO: 26566

Title: Biology of chronic graft-vs-host disease: Immune mechanisms and progress in biomarker discovery

Reviewer's code: 02961512

Reviewer's country: Italy

Science editor: Shui Qiu

Date sent for review: 2016-04-19 09:57

Date reviewed: 2016-06-08 20:32

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

This is a clearly written and exhaustive review. I have no criticisms.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Transplantation

ESPS manuscript NO: 26566

Title: Biology of chronic graft-vs-host disease: Immune mechanisms and progress in biomarker discovery

Reviewer's code: 03634913

Reviewer's country: Germany

Science editor: Shui Qiu

Date sent for review: 2016-04-19 09:57

Date reviewed: 2016-06-09 17:19

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

COMMENTS TO AUTHORS

The review "The Pathobiology of Chronic Graft-versus-Host Disease" comprehensively describes several aspects of the cGvHD. It is an important medical topic and the statement of increasing incidence of cGvHD meets our clinical observations. The cGvHD is still one major challenge after hematopoietic stem cell transplantation associated with significant reduction of quality of life or even fatal outcome. The tables of the article are informative and give a good overview of the symptoms, involved cell types and potential biomarkers of cGvHD. Due to the importance of animal models for further research, a more detailed description of the mouse strains (including H-2 haplotypes) for cGvHD induction would be useful. However this is only a minor point since the topic of the manuscript is the pathobiology of cGvHD in general. In the biomarker section information about potential cellular biomarkers (e.g. CD4 or CD8 T cell levels) could maybe an addition to the important bundle of the described cytokine/protein based markers. Overall, the manuscript represents a very well done review including all key aspects of the cGvHD. I clearly recommend this article for publication.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Transplantation

ESPS manuscript NO: 26566

Title: Biology of chronic graft-vs-host disease: Immune mechanisms and progress in biomarker discovery

Reviewer's code: 03472898

Reviewer's country: United States

Science editor: Shui Qiu

Date sent for review: 2016-04-19 09:57

Date reviewed: 2016-04-27 04:37

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

This is a well written paper on a very complex issue. I do not see the relevance in the figure and would omit it. On p. 7 near the bottom there is a grammatical error. This manuscript is well thought out and planned. Flow is acceptable and easy to follow. This is a good review. I am not sure how much of this is new information but this is a relevant topic in transplant. Some references are not recent.