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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Transplantation
ESPS manuscript NO: 26201
Title: Pharmacological Tie2 activation in kidney transplantation
Reviewer's code: 00591996
Reviewer's country: Taiwan
Science editor: Fang-Fang Ji
Date sent for review: 2016-03-31 10:55
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[Y] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Summary Using a murine MHC-mismatched renal transplant model, the authors demonstrated that exogenous activation of Tie2 with vasculotide (VT) was graft-protective as reflected in significantly diminished expression of peritubular and glomerular endothelial adhesion molecules, infiltration of inflammatory cells, fibrogenesis, and improved survival rates after kidney transplantation. Overall, it is a meticulous study with the inclusion of adequate parameters in a technically challenging animal model to elucidate the point that Tie2 activation promotes an anti-inflammatory, pro-survival, and anti-permeability phenotype of the vasculature. On the other hand, some issues need to be clarified.

Major comments 1. In the introduction section, ischemia-reperfusion injury (IRI) and acute rejection, which are two different causes of graft injury after organ transplantation, were mixed up. The authors may discuss them separately. On the other hand, since the topic is about rejection, why bother to discuss IRI in the first place? If a transplantation group using C57Bl/6 mice as both donors and recipients, the effect of IRI could theoretically be taken out of the picture. The issue can then be focused on acute rejection itself. Besides, parameters for monitoring IRI (e.g., myeloperoxidase, oxidative stress) were not included and the animals were not sacrificed at an acute time point for this

purpose. 2. The dosage of VT used in this study (i.e., 500 ng) should be justified and referenced. 3. Information about the number of animals used and animal grouping should be made available to the readers in the Methods section. Did the experiment include C57Bl/6 to C57Bl/6 transplantation to serve as controls? 4. In the Methods section, the authors mentioned that "Cold ischemia time is 60, and warm ischemia time 30 minutes. After explantation, kidneys are stored in vehicle solution at 4°C for 45 minutes…". Since cold ischemia time is defined as the time between the chilling of a tissue, organ, or body part after its blood supply has been reduced or cut off and the time it is warmed by having its blood supply restored, it seems that the procedure did not quite match the definition. Ina addition, warm ischemia time, which is the time a tissue, organ, or body part remains at body temperature after its blood supply has been reduced or cut off but before it is cooled or reconnected to a blood supply, was just 30 minutes according to the authors. Does it mean that all vascular reconstructions were finished within 30 minutes? That would be really amazing! Congratulations if it was the case. The authors may just confirm the correctness of the data. Minor comments 1. Since serum creatinine and urea levels are not sensitive indicators of changes in renal function, it is generally suggested that metabolic cages should have been used to collect urine for computing changes in glomerular filtration rates for small animals. On the other hand, taking into account the technical difficulty of the procedure, the authors had already done a nice job. 2. Regarding the dearth of murine renal tissue from each mouse that may not be enough for Western blotting, this author is wondering whether the authors used tissue pooling for analysis in this aspect? The information should be available to the readers.

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		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

This is an interesting study in which authors show that vasculotide -a synthetic Tie2 agonist- may improved renal transplant outcome. I suggest that: 1. A sentence regarding the effects of the different angiopoietin ligands (agonistic, antagonistic) could be added after citations 6,7) in the second paragraph of the introductionto 2. Authors describe more in detail the aims of the study. For instance after the last sentence of the introduction, perhaps they could explain how they evaluate the protective effects of vasculotide (for instance "...., assessing inflammatory infiltration, fibrous tissue deposition, ... renal function and survival". 3.It seems that some results do not reach statistical significance due to a type II error. A sentence relative to this possibility should be added in the discussion. 4. Some results could be better defined (i.e.,"immense", "profound")