

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

ESPS manuscript NO: 26990

Title: Stem cell therapy for the treatment of leydig cell dysfunction in primary hypogonadism

Reviewer's code: 01236209

Reviewer's country: China

Science editor: Jin-Xin Kong

Date sent for review: 2016-05-03 19:05

Date reviewed: 2016-05-06 15:49

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"/> 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 checked="" 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

The manuscript introduced the background of hypogonadism, and discussed two major types of stem cell therapy for hypogonadism. One is to transplant adult Leydig cells from stem cells of various origins from bone marrow, adipose, or embryonic sources. The other is to isolate stem Leydig cells, amplify and differentiate into adult Leydig cells in vitro, and transplant the resulting adult Leydig cells back to testis. In addition, the authors also proposed a third possibility that is to activate stem Leydig cells in vivo for primary hypogonadism due to age. In general, this review covers an interesting topic in the stem cell field, and is well written. I only have a few minor comments: (1) The sentence "The second method involves isolating, identifying, and transplanting stem Leydig cells into testicular tissue" (in the Abstract) is inaccurate. (2) In addition to the third strategy proposed by the authors, namely in-vivo re-activation of SLCs in men with primary hypogonadism due to age, derivation of SLCs, rather than adult Leydig cells, from various stem cells might overcome the growth arrest issue. This strategy might facilitate long-term transplantation, and be applicable to more hypogonadism patients. (3) Some grammar errors, such as page 3, "From



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its role in the growth of genital organs in utero, to the initiation of spermatogenesis and the development of secondary sexual characteristics during puberty, testosterone is essential to biological function"; page 3, "among others"; page 5, "Thereafter, another regression of fetal Leydig cells occurs, each reaching a nadir at one year of age"; page 5, "that these cells must play a significant role in this embryologic question"; page 14, "whether through aging or toxic exposure".



ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

ESPS manuscript NO: 26990

Title: Stem cell therapy for the treatment of leydig cell dysfunction in primary hypogonadism

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<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"/> No	<input checked="" 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

Because of the limit reports of researches on MSC-based cell therapy for hypogonadism, this review could not provide new principle and mechanism in the application of MSC already known in the treatment of diseases other than hypogonadism. I do suggest the authors to summarize something new and special in the differentiation induction or pretreatment of MSC before cell transplantation, animal models, and regimen of cell therapy including grafting route, cell amount, times. One more table could be added to show different cocktail formula for Leydig cell differentiation in vitro. Stem Leydig cells hold great potential in cell therapy. In order to isolate cells for in vitro manipulation or to reactivate in vivo to repair damage or dysfunction, the location of stem cells in testis, their immunophenotypes and possible reactivation process are questions required to be answered. It will be helpful if more detail information can be presented in this aspect.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

ESPS manuscript NO: 26990

Title: Stem cell therapy for the treatment of leydig cell dysfunction in primary hypogonadism

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" 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
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<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

The manuscript reviewed relevant progress on stem cell therapy for the treatment of Leydig cell dysfunction in primary hypogonadism. The writers discussed this interesting topic from normal Leydig cell dysfunction, stem Leydig cells, Leydig cell dysfunction to stem cell therapy. To sum up, the manuscript has a specific framework especially in summarizing preclinical trials about differentiation of stem cell lines into steroidogenic Leydig-like cells (Table 1). And I recommend it a good systematic review for stem cell treatment for Leydig cell dysfunction. A few comments are as follows: (1) In the part of "Leydig Cell Dysfunction", some cited references are relatively old to illustrate probable mechanisms of Leydig cell dysfunction. If possible, I hope the manuscript could offer a few recent trials related to mechanism research. (2) As the title is "Stem Cell Therapy for the Treatment of Leydig Cell Dysfunction in Primary Hypogonadism", I think the writers should retrench the first four parts and provide more information in the part "Stem Cell Therapy", especially in possible reactivation process for SLCs. (3) More research progress on Leydig cell derived from umbilical cord should be added in the part "Stem Cell Therapy", as the manuscript had discussed



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BMSCs and ADSCs in detail.