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PEER-REVIEW REPORT

Name of journal: World Journal of Biological Chemistry
Manuscript NO: 33436
Title: Identification of neuron selective androgen receptor inhibitors
Reviewer's code: 03259512
Reviewer's country: Bosnia and Herzegovina
Science editor: Xiu-Xia Song
Date sent for review: 2017-02-12
Date reviewed: 2017-02-20

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] 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

Authors describe the thiazole class of antibiotics as compounds able to inhibit AR activity in a neuronal cell line but not a muscle cell line. One of these antibiotics, thiostrepton was shown to inhibit AR activity in neuronal GT1-7 cells with nanomolar potency. The conclusion is that thiazole antibiotics can inhibit AR selectively in motor neurons, thus, can be used as treatment or prevention of spinal and bulbar muscular atrophy (SBMA) symptoms. The article is interesting, well written, and data looks reliable and novel. However, few important points require detailed clarification/additional data. Thiazole antibiotic Thiostrepton has been shown to down-regulate the transcription factor FOXM1 and, thus, the AR inhibition might be also indirect in vivo or in cell based screening. Authors should clearly indicate that fact all over the manuscript and discuss their data in the light of AR indirect inhibition. In other words, authors should discuss the inhibition of AR signaling pathway by means of blockade of potential upstream regulation by transcription factor. The authors should also stress that point in the study, and discuss the possibility of further testing of direct

binding of thiazole antibiotics to AR (using other assays, like competitive binding etc). Established FOXM1 downstream targets (independent from AR signaling) were not assessed. Limitations of the study were not discussed. In the Abstract - I suggest to replace words "… AR activity", "…AR antagonism ..", "…AR selectively in motor neurons.." with " AR conformational transformation…", or "… AR signaling .." or "AR pathway signaling", or " AR indirect blockade mediated by transcription factor FOXM1 etc …" or similar in the meaning phrases. The current stage of abstract is partially misleading/confusing, and gives an impression of direct antagonist-receptor inhibition that in fact was not completely proven. Methods: "…intensity of FOXM1 expression creating a scale ranging from 0-2"(page 8). It is very short description of the scoring. You have to provide more details and also provide images with highest expression score and with lowest as supplementary data. Figure 3. Statistical analysis of protein expression should be presented. Usually westerns are repeated 3-4- times, and all protein bands (band intensities) mean values are assessed and deviations are calculated and organised as bar graphs or similar for 5 of controls. In Figure legend it is not mentioned how many times the experiments were repeated. P84 expression is not equal, please provide a statement about amount of protein loaded for different cell lines. Figure 4. Nuclear images for the lower panel (DHT + Thios..) look distorted. Why the nuclei are so long and different from the rest of the nuclei in the above images? The cells nuclei look smudged. % of co-localization should be also calculated fro several images (experiment was supposed to be repeated for 3-4- times) and presented as graph with error bars. Figire 5. Magnified images should be included as the presented magnification/images give very little information about cellular/intracellular/nuclear localization of the AR. Nuclear co-localization/ or translocation for beta-catenin should be also tested using immunofluorescence/IHC.

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PEER-REVIEW REPORT

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

COMMENTS TO AUTHORS

In this manuscript, the Authors exploited a FRET-based AR conformation reporter assay to identify AR antagonists, selectively acting on neural, but not muscle, cells. Although the Authors did not identify a compound to be tested in SBMA, thiostrepton might represent a lead compound to develop drug-like molecules, maintaining the interesting cell-type selectivity. I believe this ms should be published in its present form. I just have a minor correction/clarification to ask: in the Discussion (third Paragraph, line 6, "...determine exactly how…"), the Authors wanted probably to indicate "thiazole antibiotics", and not "antibodies". Please correct or explain.

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PEER-REVIEW REPORT

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
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		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Unfortunately page numbers and lines are not marked, rendering difficult reviewing this MS. This is an interesting study, the paper is well written and results could be potentially relevant. However, there are some problems with the resulst: 1. when describing results shown in Fig. 2C Authors should mention the fact that AR activity is lower in cells transfected with the AR with 65 stretch. 2. results shown in Fig. 3, in general, are not so clear. for intsnace the claimed different expression of FOXM1 s not so apparent in Fig. 3A (also the control p84 show variations). In Fig. 3C, the claimed decrease follwoing siRNA is also not so clear. Overall, the fact that FOXM1 mediates the ability of thiostrepton is not so stronggly evident as claimed (and conclusions in results and discussion should be smoothed in my opinion). Alternatively, the Authors could show better blots. 3. there are some problems in the description of results of Fig. 5 (some of the panles do not coincide with the description in the results).

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PEER-REVIEW REPORT

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
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		[Y] No	

COMMENTS TO AUTHORS

Journal World Journal of Biological Chemistry Manuscript Number 33436 Manuscript Title Identification of Neuron Selective Androgen Receptor Inhibitors Kennedy disease is due to an activation of a polyglutamine tract-expanded androgen receptor (AR), that causes spinal and bulbar muscular atrophy. Systemic AR inhibitors can ameliorate symptoms in experimental models but have shown mixed results in clinical trials, probably because they provoke muscle mass decrease by inhibiting anabolic AR activity in muscle cells. The authors hypothesised that a neuron-specific inhibition of AR activity may improve efficacy. By means of a FRET-based assay of AR conformation change, they identified siomycin A, a thiazole antibiotic, as a potential neuron-selective AR inhibitor. Then, they showed that thiostrepton, which belongs to the same class of antibiotics and has been reported to function similarly to siomycin, also has neuron-selective AR inhibitor capacity via anti-FOXM1 activity. They furthered demonstrated that this activity was preferential in rat spinal cord as compared to skeletal muscle. The manuscript is very well written, easy to follow. The rationale for the study

is clear, the study design is adequate and the methodology is clearly described. The results are well presented, and the conclusions are supported by the results. I have only minor comments: 1. Figure 3 is cited in the text (page 10) before Figure 2. 2. The quality of Figure 5 B (histology) should be improved. The tissue sections seem damaged those corresponding to AR.