



SDI Review Form 1.6

Journal Name:	British Microbiology Research Journal
Manuscript Number:	2015_BMRJ_16297
Title of the Manuscript:	Descriptive analysis of Ebolavirus proteins: towards development of effective therapies
Type of the Article	Review Article

General guideline for Peer Review process:

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound.

To know the complete guideline for Peer Review process, reviewers are requested to visit this link:

(<http://www.sciencedomain.org/page.php?id=sdi-general-editorial-policy#Peer-Review-Guideline>)



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PART 1: Review Comments

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
Compulsory REVISION comments	The manuscript addresses a very timely topic and an important aspect of countering Ebola. However, it does so quite poorly and requires significant modifications. I would suggest streamlining the manuscript and abstract by 50 to 25% to focus the authors onto the most salient points and the most effective way of presenting them clearly. The title refers to "effective therapies" yet also discusses vaccines. Either cover only vaccines that show post-exposure therapeutic effects or adjust the title to "effective therapeutics and vaccines". Since the manuscript would benefit from shortening I would be inclined to remove the vaccine component unless it is greatly strengthened (see comments below). The references cited in the text are often to the wrong publications, though some sections are more accurate than others. The introduction is particularly bad in this regard e.g. L51, L55, L62(17-25 don't belong here). L67 refs 1,27 could benefit from more recent references in light of the larger number of cases occurring. L93 needs the more recent Kuhn works on nomenclature. This is a major problem throughout many other sections too. Also, it is customary in a review to refer to the original work if addressing a topic in detail rather than citing other reviews. The latter is usually left for areas that are	Both the manuscript and abstract have been reduced by almost 50%. The whole document has been reduced from 40 pages to 23 pages. The title has been adjusted to Descriptive analysis of Ebola virus proteins: towards development of effective therapeutics and vaccines (see line 2, 3). Thanks for your valuable advice. We have added a brief description of EBOV proteins to the introduction (see line 34-45) with few primary references (see reference 1-6). Recent references to highlight the morbidity and mortality rate of the current EVD outbreak have been added, see ref. 1. Correct references on nomenclature have been added (see reference 9 and 10 and Table 1).



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	needing mention yet outside the in depth scope of the manuscript. L178-L181 repetition here. L198, does GP interact with NP? L223, sufficiently due? L278, that, “allow the immune system to recognise infected cells”, #17 wrong ref. Be more explicit here? L318-324, move to bat section if there should be one. This needs more work and would need a lot more in depth analysis of the potential parallels to bat immunity. L421-435 perhaps focus more on the known mechanisms such as macropinocytosis and these are published and so lead entry with L476 theme. L55- the nomenclature of the Filoviruses has changed and a précis given of ICTV findings [Kuhn et al.] and this notation used throughout. For example L55 we have Zaire Ebolavirus, L59 we have Ebola, L68 we have Ebola Zaire, and L81 we have Ebolavirus...consistency would add to clarity. L72 Is not dehydration also a very big problem for the	We have made sure to cite only primary references and Books. Citations from review articles have been removed unless otherwise. References have been reduced from 218 to 175. L178-181 has been deleted. No. We erred. L198, has been deleted. ‘Sufficiently’ has been deleted. See line 128. L277-L324 & ref 17 have been deleted. Part of topic is covered under ‘future perspectives’. L318-324 has been deleted. Bats are discussed under future perspectives (see line 660-681). A proper review on bats & EBOV will be written in due course We agree with you and appreciate your suggestion. However, since it is a review, we thought giving both sides of the story would give the readers a correct picture. See line 190-212 Thank you so much. We have updated the Filovirus nomenclature. See line 67-78 and Table 1. See also ref. 9-10. We have also addressed the issue on Ebola virus throughout the document. Yes it is. Thank you. We have included it in line 57.
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	patient? L73 and elsewhere L996, L1013 is not adequately justified. Just because a patient generates antibodies to non-structural proteins, it does not necessarily mean that they are neutralizing, just that epitopes are foreign. To date only specific GP specific antibodies have shown efficacy since they can bind epitopes that are exposed on the virion and can disrupt receptor binding or a post endocytic stage by interfering with GP1/GP2 disassembly/the membrane fusion process. In vivo, targeted cell surface displayed GP may also herald the ADCC system to destroy virus infected cells. Therefore L73 associating natural recovery with appearance of antibodies would benefit from insertion of, “neutralising antibodies to specific viral proteins” rather than, “antibodies specific for Ebolavirus proteins”. Consequently L31 of abstract, L827 and elsewhere is not really justified. It is the case with many antibody based therapies that a carefully chosen GP/coat protein binder can mediate neutralization and that one may not benefit from diluting the therapeutic antibody with non-neutralizing binders. L865 wrong reason for using these antigens is presented. More importantly GP can generate neutralizing antibody responses and NP can generate neutralising T-cell responses. Can other internal antigens be leveraged to generate potent T-cell responses and would these augment existing vaccines? L76- is this true? Surely much of the pathology can be attributed to other more direct factors. L102 and elsewhere there is inconsistency about the	We have included the word, ‘neutralising’ antibodies where appropriate. See line 22, 173, 176, 393, 536 etc Thank you so much. We agree with you. We have removed the statement as it was misleading. Agreed and reason deleted. Yes. VLP vaccines that have VP40, NP and GP may be able to induce T cell responses to augment virus vectored vaccines. Thank you. Statement was misleading indeed. We deleted it.
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	nature of the nucleocapsid, here it skips VP35 and L. L114 manipulation not appropriate word here, perhaps processing? NP and L have minimal coverage of therapeutics yet it is the case that both have relatively advanced countermeasures now. I would suggest shortening and sharpening the descriptive for each target and antigen using that space saving to cover the therapeutic options for each. I would also encourage the use of a figure for the protein and the possible approaches to neutralise it. For example GP trimer with the Zmab binders showing locations and what processes they block. For an internal antigen, the same and or a pathway that could be interfered with. Well thought out figures would convey a clearer message. Figure b is of poor quality, it is not particularly representative of the particle based on what is known [see Bharat references on tomography], no VP35 and L. L167 is GP type I or type II as in abstract it says type II. L788 how can VP40 and VP24 be linked to the ribonuceoprotein complex at the inner surface of the lipid bilayer? (again wrong reference cited) L870 onwards- Ad vaccine can use other serotypes (Crucell), or Ad from other species (chimp), or different delivery route (Maria Croyles work) to bypass pre-existing Ad5 immunity. Vaccine section would also benefit from consideration of challenge dose and route and what vaccines have been	Thank you so much. We have Rectified the inconsistency. See line 40-41, 81,91-92, The paragraph containing this word, 'manipulation', was deleted as it was not important. We have added more information on therapeutics and vaccines targeting NP and L. See line 435-450; 465-476. See Table 2 and figure 2 Thank you. Descriptive analysis of each EBOV protein was shortened and more therapeutic options targeting these proteins has been added. See line 435-584. We have also added figure 2 to highlight the sites within EBOV proteins and EBOV replication cycle targeted by promising therapeutics. See Figure 2. Thank you so much. Figure 1a and 1b were deleted. The description given in line 67-88 is adequate for describe the basic structure of EBOV. Thank you. It is type 1. See line 95 This was indeed an error by one of the review papers we had used. The statement & reference have been deleted. Thank you so much for the references. The information has been added in the revised manuscript. See line 397-400. References by Maria Croyle have been added. See references 125-127
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	compared side-by-side with low pass virus stocks that have retained pathogenicity as opposed to isolates that have been passed in vitro many times over to the detriment of in vivo pathogenicity. L953, poor description of chimeric nature of these antibodies. L961-L971 redundant section. L973 et al., repetition L997 unethical without a lot more laboratory based studies. L1099 section not warranted, perhaps mention that combinations can be more efficacious but each one must be tested carefully. L1136 not necessarily true that antibodies are the major players in enabling bats to survive infection without apparent disease. It may well be a combination of factors, especially innate immune responses. No mention of screening small molecule libraries to get therapeutic leads. No mention of studies using previously cleared FDA approved drugs as novel therapies for cross-purposing to cut down costs *. No mention of drugs modulating host function that are critical for viral assembly that might be useful (can be	Noted. Table 2 has been added to show the administration route only of current vaccines. See line 431-432. We could not add the challenge dose as the latest paper we saw was for 2011, we think that a latest paper would have been better. More information has been added to describe these antibodies, See line 491-537. We have added a sentence to show the papers where the chimeric nature of the antibodies are described, See line 512-513. Redundant section has been removed. Repetition has been deleted We have rephrased the sentences to make them ethical as these are just suggestions meant to stimulate further thinking and research see line 645-658. We have removed the section in L1099 and mentioned the potential efficacy of combinations. See line 645-658, 623-625 We Agree, thank you. The statement has been rephrased and more information has been added. See line 660-681 Thanks for the reminder. We have now included Small molecule libraries in line. All the potential drugs have been described. See also line 539-567 and figure 2 Agreed. Drugs modulating host function have been added. See line 569-584 and Figure 2
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	mentioned with *) Ethical issue L997 might be seen as unethical in proposing these experiments without good laboratory based evidence that it is a valid approach.	Yes/NO. The statement has been rephrased. See line 645-658. These are research statements meant to stimulate further thinking and research.
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<u>Minor</u> REVISION comments	Grammar and typography need attention throughout. Examples include, but are not limited to: L7- Nucleoprotein>nucleoprotein EBOV abbreviation is provided early on yet is not used consistently L25- Antiobdy>antibody L12 EBOV's> EBOV particles Use of paragraphs to break up portions of text focusing on different aspects would be helpful, e.g. L65 the disease could be a different paragraph, L882 discussion of VSV etc... L79, some data from Kawaoka lab suggesting a small amount of sGP might be structural? L79, synthesise data is not a good choice of words, perhaps summarise would be more appropriate. References need a standard format.	We have carefully strived to edit the typography and grammar. Corrected. Rectified and EBOV is used consistently in the revised documents. Corrected. Corrected throughout the revised manuscript Majority of paragraphs have been broken down. Yes. They suggested that sGP can substitute for GP1, forming a sGP-GP2 complex and conferring infectivity. We have not included it in this review Corrected. See line 60 References have been standardised. See line 693-1059
<u>Optional/General</u> comments		