



SDI Review Form 1.6

Journal Name:	International Journal of Biochemistry Research & Review
Manuscript Number:	Ms_IJBCRR_23216
Title of the Manuscript:	Optimizing the aggregation propensity of therapeutic monoclonal antibodies against cancer and autoimmune diseases: a computational study
Type of the Article	Original Research 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>)



SDI Review Form 1.6

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	This manuscript describes a computational approach to optimize the aggregation propensity of therapeutic antibodies. The following issues need to be addressed. 1. This computational approach can be applied to any kinds of therapeutic antibodies, not specifically to anti-cancer and anti-autoimmune diseases. As such, the title should be changed to "Optimization of aggregation propensity of therapeutic antibodies by a computational approach". 2. The abstract should be concise and focused to the topic. The topic of this manuscript is optimization of the aggregation propensity of therapeutic antibodies. A little is related to antibody half-life and low stability, which mainly result from antibody degradation. Therefore, the sentence "Despite their benefits, mAbs obtained from human or other sources have deficiencies such as short in vivo life and low stability." in the first paragraph of abstract should be deleted. 3. The detailed information for each antibody therapeutic function/mechanism in the Supplementary Material is useless for this study, since there is nothing related between antibody function and antibody aggregation-prone propensity. Therefore, this information should be deleted. One table of the summary of these antibodies is enough. 4. As authors stated, CDRs of antibodies are very important for the antibody-antigen binding function. They should be kept unchanged in the "mutated" version. Unchanged CDRs means not only the sequences, but also the conformations. If the CDR conformations are changed and even their	We sincerely thank the reviewer for his/hers detailed constructive criticism and comments, which is gratefully acknowledged in the "Acknowledgements" section of the manuscript. 1. We prefer not to change the title of the manuscript since the work was done on mAbs against cancer and autoimmune diseases. It is true that the work can be generalized to any kinds of therapeutic antibodies and we are in the process of verifying that (work in preparation), but we have no concrete answers yet. 2. This sentence was removed from the abstract 3. Following the reviewer's comments, we removed detailed information for each antibody and we now provide Tables 1 and 2, containing information about the antibodies used. 4. Special care was taken that the conformations of the CDRs remain unaltered with the "mutations"



SDI Review Form 1.6

	sequences unchanged, the antibody antigen- binding function will be gone. The CDR conformations are supported by frameworks in the variable regions. When the framework sequences are changed, CDR conformations may change. In this manuscript, the authors changed some residues in the framework sequences in order to reduce or eliminate the antibody aggregation propensity. Although the authors did confirm the conformations of the whole antibody molecule unchanged before and after mutations, it was still unable to ensure the local structures, 6 CDR conformations unchanged after mutations. The appropriate way to check whether CDR conformations are changed or not before and after mutations is to compare the 6 CDR conformations between the mutated and native versions using antibody structure modeling software. If this kind of data was available, it would be more convincing. 5. It seems like the authors had a little to discuss in the Discussion Section. Actually there are many topics discussable, such as the followings: (1) The mechanisms of protein aggregation are very complicated. There are at least 5 mechanisms reviewed in some literatures. What is the main mechanism for antibodies to be prone to aggregation? (2) There are more mAbs available on the market than those chosen by the authors for this study. Which kind of criteria did the authors use to choose these antibodies for this study? (3) There are quite a few of computational approaches published for protein aggregation- prone region prediction using different algorithms. Although the algorithm, AMYLPRED2, which the authors used in this manuscript was published in the past, it would be much helpful to the audience if the authors could give a little information of the AMYLPRED2 and the features as compared to some others. (4) As we know, there are some publications available regarding antibody aggregation-prone predications, such as the Ref 29 listed in the manuscript. When the authors stated,	made and this has been checked carefully with modeling software and it is now mentioned clearly in the “Discussion” section of the manuscript, and also in the “Materials and Methods” section, “Novel models”. 5. Thanks to the reviewer’s comments we have now re-written the “Discussion” section of the manuscript , answering most points raised (in yellow). We should say that the manuscript has now been improved considerably and we are grateful to the reviewer for his/hers very constructive criticism and precise review. 6. We have tried to correct all errors and typos that could identify.
--	--	---



SDI Review Form 1.6

	“we discovered some common groups of ‘aggregation- prone’ regions in the amino acid sequences of the antibodies that are present in almost all the monoclonal antibodies that are now on the market (29)” on the page 5, how much difference of the predicted aggregation-prone regions between the two algorithms? By the way, there is a grammatical error in this sentence. “that” in the sentence of “...the antibodies that are present in almost...” should be deleted. 6. The manuscript suffers from a large number of errors including grammatical, editorial, and formatting errors. The manuscript should be re- read carefully and checked for all errors and reworded for some phrases by native English speakers.	
<u>Minor</u> REVISION comments		
<u>Optional/General</u> comments		