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# In Silico Evaluation of Two Targeted Chimeric Proteins Based on Bacterial Toxins for Breast Cancer Therapy

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**Associate Editor's Comments:**

We are very excited to have been given the opportunity to revise our manuscript. Thank you for advices, which will help us improve it to a better scientific level. We have revised the manuscript according to the editor report and reviewer comments by red line, and the proposed changes have taken place. It is our belief that the manuscript is improved after making the suggested editions and we hope our revisions meets your approval.

*Associate Editor 1:*
*This manuscript describes a study on "evaluation of two targeted chimeric proteins based on bacterial toxins for breast cancer therapy" using in Silico methods. Points to address are:*
*1. The authors have hypothesized that adding toxic molecules such as a Shiga toxin and Pseudomonas exotoxin A may improve the efficacy of monoclonal antibodies in breast cancer. They have used in silico methods to prove this hypothesis. But they have not provided any reference to why they have this hypothesis? What is the scientific background of this hypothesis?*

***Response:*** Thanks in advance for the valuable comment

MAbs used for targeting and bind to target reseptor and then toxin moiety deliverd to cell. For example SS1(dsFv)PE38 recombinant immunotoxin contains the variable domains of murine MAb SS1 that fused to PE38. SS1 MAb binds with high affinity to mesothelin in ovarian and pancreatic cancers cancers.
We used *in Silico methods* to ensure the new chimeric structures attached to the target reseptor and the lack of a change in the structure

*2. In the introduction section, the authors have mentioned that "the efficacy of trastuzumab is not ideal and have many side effects including attenuated DNA repair, prevention of cleavage of HER2 extracellular domain (ECD), induction of antibody-dependent cell-mediated cytotoxicity (ADCC), declined intracellular signal transduction and antiangiogenic consequences have been attributed to the administration of this medication"! These are not side effects of trastuzumab, rather they are considered to be alternative mechanisms of action of this monoclonal antibody.*

***Response:*** We sincerely thank the reviewer for careful and thorough reading of this manuscript and for constructive criticisms and valuable comments, which were of great help in revising the manuscript. The correction was done

*3. It is necessary that the authors perform some analysis on the effect this chimeric protein on breast cancer , at least in vitro. Otherwise, we cannot process it any further, or they can send the manuscript to a biotechnology journal.*

***Response:*** Thanks for the valuable comment. In- vitro tests were done and the other article was written and under review

*4. In the discussion section, the authors should compare the results of the current study to other published studies findings.*

***Response:*** As suggested by the reviewer, for better understanding of reader the results of the current study should compare to other published studies findings.

Previously keshtvarz etal ,design and evaluate PE38-P4A8 chimer immunotoxin that by Codon Adaptation Index 0.94 and GC percentage 54.2 optimized and revele high and stable expression in bacterial cells. the most second structures were random coils and disordered regions also secondary structure of this immunotoxin was stable. the construct was hydrophilic and acidic. tertiary structure of the fusion protein by C-score -3.36 contained the highest C-Score. In this study ASGGPE and (G4S)3 linkers were used to isolate different segments. in another study Imani-fooladi etal,design and analysis TGFαL3-SEB fusion protein that by CAI index 0.85 optimized and by GC content 44.06% the overall stability of mRNA increased. the coil structural content was high. TGFαL3-SEB fusion protein was hydrophilic and the computed isoelectric point was 7.72. tertiary structure of the fusion protein by C-Score -0.42contained the highest C-Score. Comparing these two chimer proteins proposed that TGFαL3-SEB and PE38-P4A8 were stable fusion proteins with proper affinity to their receptors that overexpressed in cancer cells.

***Kind Regards,***

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