Dear Editor,

Thank you for the consideration of our manuscript entitled "Protein WISDOM: A Workbench for In Silico De novo design Of bioMolecules" for the Journal of Visualized Experiments. The aim of *de novo* protein design is to find the amino acid sequences that will fold into a desired 3-dimensional structure with improvements in specific properties, such as binding affinity, agonist or antagonist behavior, or stability, relative to the native sequence. Protein design lies at the center of current advances drug design and discovery. Not only does protein design provide predictions for potentially useful drug targets, but it also enhances our understanding of the protein folding process and protein-protein interactions. Experimental methods such as directed evolution have shown success in protein design. However, such methods are restricted by the limited sequence space that can be searched tractably. In contrast, computational design strategies allow for the screening of a much larger set of sequences covering a wide variety of properties and functionality. We have developed a range of computational *de novo* protein design methods capable of tackling several important areas of protein design. These include the design of monomeric proteins for increased stability and multimeric proteins for increased binding affinity. For the dissemination of these methods for broader use we present Protein WISDOM (http://www.proteinwisdom.org), a tool that provides automated design methods for a variety of protein design problems. Structural templates are submitted to initialize the design process. The first stage of the methods is an optimization sequence selection stage that aims at stability through minimization of free energy in the sequence space. Selected sequences are then run through a fold specificity stage and a binding affinity stage. A rank-ordered list of the sequences for each step of the process, along with relevant design structures, provides the user with comprehensive quantitative assessment of the design.

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We appreciate your time and consideration of this manuscript for publication, and are looking forward to receiving your comments.

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