Computational Design of Functional Proteins for Biomedicine

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Abstract

Finely orchestrated protein activities are at the heart of the most fundamental cellular processes. The rational and structure-based design of novel functional proteins holds the promise to revolutionize many important aspects in biology, medicine and biotechnology. Computational protein design has led the way on rational protein engineering, however many of these designed proteins were solely focused on structural accuracy and completely impaired of function. At the methodological level, I will present a computational design strategy centered on the exploration of *de novo* protein topologies and the use of structural flexibility with the ultimate goal of designing functional proteins. This approach aims to solve a prevalent problem in computational design that relates to the lack of optimal design templates for the optimization of function. By expanding beyond the known protein structural space, our approaches represent new paradigms on the design of *de novo* functional proteins.
We thus far have focused on using such computational method for structure based vaccine design. Vaccines have proven to be a successful approach to control and eliminate important infectious diseases. However, a number of pathogens still lack clinically approved vaccines, highlighting the limits of classical vaccine development. Following the strategy of reverse vaccinology, we focus on employing methods from computational protein design and structural vaccinology to engineer novel immunogens that enhance the induction of neutralizing antibodies.

Recently, a first proof of principle has shown that a computationally designed protein presenting the Respiratory Syncytial Virus (RSV) Motavizumab epitope elicited potent anti-RSV neutralizing antibodies in nonhuman primates. I will also show biochemical, biophysical and immunological characterization of the computationally designed immunogens. Notably, we have optimized the immunization conditions for the epitope-focused immunogens, with which we can elicit neutralizing antibodies in a standard mouse model. This result will enable the iterative optimization of epitope-focused immunogens based on *in vivo* immunological evidence.
These developments give rising hope for the rational development of precision vaccines focused in specific epitopes and could be transformative for pathogens that have resisted traditional vaccine development strategies.

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