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Computer Design Yields Better, More Efficient Therapeutic for Preventing Tissue Damage

(Philadelphia, PA/Princeton, NJ) - The tedious laboratory trial-and-error method for refining protein/peptide-based medicines could be accelerated and complemented by an innovative in silico (on computer) protein design method, according to researchers at **Princeton University**, the **University of Pennsylvania School of Medicine**, and the **University of California at Riverside**.

Their findings, appearing in a recent issue of the Journal of the American Chemical Society, could drastically decrease the time it takes to move potential biopharmaceuticals from the drawing board to the drug store. In this study, the researchers modeled a peptide (a chain of amino acids, such as a protein or protein fragment) called Compstatin, which prevents the autoimmune-mediated damage of organs during transplantation, and various inflammatory diseases. The computer modeling and optimization process cut down on trial and error and created a version of Compstatin seven times more efficient and stable than the original.

Since the function of a peptide depends on its form, the researchers modeled the effects of substituting each of Compstatin's 13 amino acid subunits with a different amino acid. The novel in silico sequence design method could then model how the altered amino acid sequence folds together in comparison to the original peptide.

"It is a major challenge to design new peptides and proteins that exhibit the desired function such as improved inhibition for the complement system. The challenge centers around the problem of selecting promising sequences from the huge number of possible combinations and making sure those sequences will have the desired three-dimensional structure," said Christodoulos A. Floudas, PhD, a Professor of Chemical Engineering at Princeton University, whose laboratory

developed the in silico de novo protein design approach. "At the heart of this innovative technology is a unique two-stage computer protein design method that not only selects and ranks sequences for a particular fold, but also validates the stability and specificity of the fold for these selected sequences."

"It would have taken us years to synthesize and screen the 80 quadrillion possible peptide sequences that the protein design program considered," John D. Lambris, PhD, a professor in Penn's Department of Pathology & Laboratory Medicine and a co-author on the study whose laboratory had discovered Compstatin in 1996. "In the end, we came up with two analogues to Compstatin - each created by altering one amino acid - that performed its job even better than the original protein."

Compstatin works by blocking human complement, the immune system's passive alarm network that detects pathogens in the blood. Unfortunately, complement can also attack healthy tissue, and a variety of diseases are associated with complement gone awry, such as multiple sclerosis and hemolytic anemia. In addition, complement is thought to play a role in the destruction of cells during strokes, heart attacks, and burn injuries. The complement reaction is actually a series of interlocking cascades, or chain reactions, of biochemical events involving at least 30 proteins. Compstatin works by preventing the activation of C3, a protein that functions at the point where all the complement protein cascades intersect.

The two Compstatin analogues derived from the experiment are superior in their ability to cling to and, hence, prevent the activation of the C3 complement protein. Based on these two analogs, more Compstatin analogs have since been designed, some of which are 200 fold more active that the original Compstatin, according to Lambris. These new Compstatin analogs will be further refined and tested until ready for clinical trials.

To create templates of the desired shape for Compstatin, Dimitrios Morikis, PhD, a researcher at the Department of Chemical and Environmental Engineering of University of California, Riverside, identified the three-dimensional structure of Compstatin in solution via nuclear magnetic resonance (NMR) experiments, which he then computationally refined.

The computational de novo protein design system, developed at Princeton University by Floudas and postdoctoral associate John Klepeis, is a technological advance made possible by (i) a novel mixed-integer optimization model that narrows 200 trillion amino acid sequences into a short list of candidates that are likely to produce a peptide of the desired shape, and (ii) a system called ASTRO-FOLD that, using first-principles, predicts the structures that would be formed by the candidate sequences. The second step confirms and refines the first.

A distributed computing environment consisting of eighty Linux-based computers was used for all the computational predictions, and the predicted new peptides were subsequently synthesized and experimentally validated in the Lambris laboratory at Penn.

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Editor's Note: Dr. John D. Lambris and the University of Pennsylvania hold the patent for Compstatin.

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