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Researchers conduct systematic testing of deimmunized biotherapeutic agents

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By establishing protein design algorithms that simultaneously optimize drug candidates for both decreased immunogenic epitope content and high level stability and activity, Dartmouth's Norris Cotton Cancer Center investigator Karl Griswold, PhD, and his collaborator Chris Bailey-Kellogg, PhD, have established a novel testing platform. Published in *PLOS Computational Biology*, the paper, titled, "Mapping the Pareto Optimal Design Space for a Functionally Deimmunized Biotherapeutic Candidate," guides biotechnologists toward protein designs that function appropriately using sophisticated design algorithms.

"Protein deimmunization has proved important for a number of promising drug candidates, including potent anti-cancer immunotoxins that are now progressing through clinical trials," said Griswold. "Intuition suggests, and our design algorithms predict, that development of increasingly deimmunized biotherapeutics comes at the cost of progressive loss of molecular function."

To explore these putative tradeoffs, the Dartmouth team deimmunized the catalytic component of Antibody Directed Enzyme Prodrug Therapy (ADEPT), which is an experimental anti-cancer treatment. A systematic analysis of 18 deimmunized drug candidates revealed that experimentally measured molecular fitness mapped surprisingly closely onto the computational design space. This showed the potential to predict and design tradeoffs between a protein's immunogenic potential and molecular function.

"Biotherapeutics are revolutionizing modern medicine, but the fact that protein drugs are susceptible to immune surveillance in the human body represents a barrier to development and large scale deployment of even more of these powerful medicines," explained Griswold. "Using innovative dual objective algorithms, we can guide biotechnologists toward protein designs that benefit from a reduced risk of undesirable immunogenicity while maintaining high levels of inherent activity."

Overall, the team's systematic study of deimmunized protein design space reveals there is no single global optimal solution to deimmunization of a given biotherapeutic agent. The tradeoffs between immunogenicity and functionality are an inherent part of deimmunization. Referring to the title of his paper, Griswold said, "The deimmunized drug design space is bounded by a so-called 'Pareto optimal' frontier of deimmunized candidates. These protein designs are each 'globally optimal,' but they sample to varying degrees the tradeoff between reduction of immunogenic epitopes and maintenance of therapeutic activity."

The next steps for the Griswold team include studying the ADEPT system as a test bed for validating increasingly sophisticated methods. Their upcoming paper will report on deimmunization of the same biotherapeutic candidate using a novel structure-based algorithm.

More information: *PLOS Computational Biology*, journals.plos.org/ploscompbiol … journal.pcbi.1003988

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