

Functional deimmunization of therapeutic proteins by IP² (Integer Programming for Immunogenic Proteins)

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Abstract: Non-human enzymes, peptides, receptors, and binding proteins represent a massive but largely untapped pool of biological agents with unique therapeutic potential. Unfortunately, clinical application of exogenous proteins is complicated by the fact that the human immune system frequently mounts a detrimental response against non-self biomolecules. In order to produce viable therapeutic protein candidates that are less immunogenic but still maintain wild-type stability and activity, we are developing a broadly applicable epitope deletion approach. Our algorithms identify sets of point mutations predicted to optimally reduce immunogenicity (as evaluated by T-cell epitope predictors) and maintain functionality (as evaluated by sequence potentials). While this design problem is NP-hard, we have developed an integer programming approach that works very well in practice. Our approach simultaneously accounts for all potential epitopes as well as the functional consequences of each deimmunizing mutation, reducing the risk that locally beneficial mutations will manifest globally unexpected and undesired consequences. We have applied our approach retrospectively, optimizing full-protein plans for biotherapeutic proteins that have previously been partially deimmunized via extensive experimental characterization and modification of limited segments. In general, state-of-the-art metrics rank our variants better in terms of either immunogenicity or activity, or both factors.

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