Designing Non-Immunogenic Protein Drugs

Anastas Pashov
Stephan Angelov Institute of Microbiology, BAS
a_pashov@microbio.bas.bg

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A fast growing list of protein drugs is the hallmark of the modern pharmaceutical industry. Since many of them are used to replace deficient or defective endogenous proteins, they enter the patient's organism as immunologically unknown and highly immunogenic antigens. The antibodies they elicit ultimately inhibit the function of the drug and compromise the treatment. Thus, the optimization of protein drug treatment involves dealing with the so far unknown problem of drug immunogenicity. Not all patients develop anti-drug antibodies and not all anti-drug antibodies are inhibitory. Apart from predicting better the risk for each patient, the efforts are directed also to producing less immunogenic protein drugs. For the monoclonal antibodies this means, most of all, to ensure that the constant part of the molecule is from human origin. For others, it is related to hiding parts of the molecule with a cloak of an inert polymer like PEG. The core of the problem, though, is the immunogenicity of the very protein molecule. Many groups focus on reducing the intrinsic immunogenicity of the protein by introducing mutations that make it invisible to the immune system. Obviously, such an approach carries the risk of affecting the function of the drug and the algorithm for deimmunization necessarily includes predictions and tests of the activity of the mutant drug. A brief description will be presented of the philosophy and approaches used in the development of an in silico algorithm for deimmunization of coagulation factor VIII used in the treatment of hemophilia A. Availability and performance of immunogenicity predicting tools, strategies for selecting the number and positions of the sites for mutations and the acceptable replacements as well as tools for prediction of the functional consequences of the introduced mutations will be discussed. Many constraints make this optimization problem hard and, possibly, without solution. Therefore, several additional methods will be considered at the end as failsafe strategies. These include the Epivax Janus matrix algorithm for identifying and designing dominant tolerogenic epitopes as well as epistatic networks for reducing the functional impact of the introduced mutations.