Building a Better Vaccine

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GE Zentner

Vaccines improve immunity against a given disease-causing pathogen, primarily by inducing the production of neutralizing antibodies against exposed epitopes. Vaccines are considered of the most important medical advances in the history of humanity, resulting in the eradication of smallpox, the near-complete elimination of poliomyelitis, and drastic reductions in infection rates of diseases including measles, mumps, rubella, and hepatitis (Rappuoli et al., 2011). Despite these successes, infectious diseases caused 18.5% of all human deaths as recently as 2010. This burden could be reduced by the development of effective vaccines against several major pathogens, including human immunodeficiency virus (HIV), malaria, and respiratory syncytial virus (RSV), for which successful vaccine generation has been problematic.

A new method, termed epitope-focused vaccine design, holds promise for the development of vaccines against these pathogens. In this approach, protein scaffolds containing epitopes of interest are designed using computer algorithms. The specific epitopes are chosen based on those recognized by naturally occurring antibodies isolated from patients or animal models of a given disease, with the hope that they will induce protective antibody generation in vaccinated individuals.. This reverse-engineering approach holds particular potential for the development of vaccines against antigenically diverse viruses such as HIV, influenza, and hepatitis C. To assess the potential of epitope-focused vaccine design to generate potent neutralizing antibodies, a team of researchers including Dr. Roland Strong (Basic Sciences Division) and Drs. David Baker and William Schief (University of Washington) focused on an epitope from the RSV F protein recognized by the antibody motavizumab (mota).

To design a protein scaffold containing the mota epitope, the authors used a computational protein design approach termed Fold From Loops (FFL). They chose a particular structure known as a three-helix bundle as the protein template due to its similarity to the helix-turn-helix conformation of the epitope recognized by mota. Through FFL, the researchers designed 40,000 scaffolds, eight of which were selected for human-guided optimization. One design, FFL_001, was computationally resurfaced to allow use in immune boosting or to map immune responses to the designed scaffolds. This yielded a set of “FFL_surf” designs. Six out of eight FFL designs and three out of four FFL_surf designs were efficiently produced in E. coli and showed biophysical characteristics

consistent with high alpha-helical content, in line with the use of the three-helix bundle as a template. All nine scaffolds generated the correct epitope structure to be recognized and bound by mota. The authors solved the crystal structures of free FFL_005 and FFL_001 bound to mota and found that the structures were in good agreement with the design models as well as the structure of mota.

The authors next tested the ability of the scaffolds to induce neutralizing antibodies. They assayed the binding of RSV-positive human serum to FFL_001 and found that three sera reacted with the scaffold, while all six sera reacted with RSV F protein. The authors also tested the ability of three scaffolds and a virus-like particle containing multiple copies of FFL_001 to induce RSV-neutralizing antibodies in mice and macaques. RSV-neutralizing activity was not detected in mice, but robust neutralizing activity was detected in 7 of 16 macaques after three immunizations and 12 of 16 macaques after five immunizations. The researchers then performed functional analysis of monoclonal antibodies directed against FFL_001. These antibodies showed RSV-directed neutralizing activities comparable to that of mota.

These results indicate that computationally designed protein scaffolds bearing epitopes of interest can induce potent neutralizing activity, demonstrating the feasibility of epitope-focused vaccine design. "Modern structure-based, rational drug design was conceived, in large part, as a response to AIDS. Rational structure-based, reverse-engineered vaccine immunogen design, an approach heralded by these results, has as much revolutionary promise," says Dr. Strong.

Correia BE, Bates JT, Loomis RJ, Baneyx G, Carrico C, Jardine JG, Rupert P, Correnti C, Kalyuzhniy O, Vittal V, Connell MJ, Stevens E, Schroeter A, Chen M, MacPherson S, Serra AM, Adachi Y, Holmes MA, Li Y, Klevit RE, Graham BS, Wyatt RT, Baker D, Strong RK, Crowe JE, Johnson PR, Schief WR. 2014. Proof of principle for epitope-focused vaccine design. Nature Epub ahead of print 05 February 2014.

See also: Rappuoli R, Mandl CW, Black S, De Gregorio E. 2011. Vaccines for the twenty-first century society. Nat Rev Immunol 11(12):865-872.

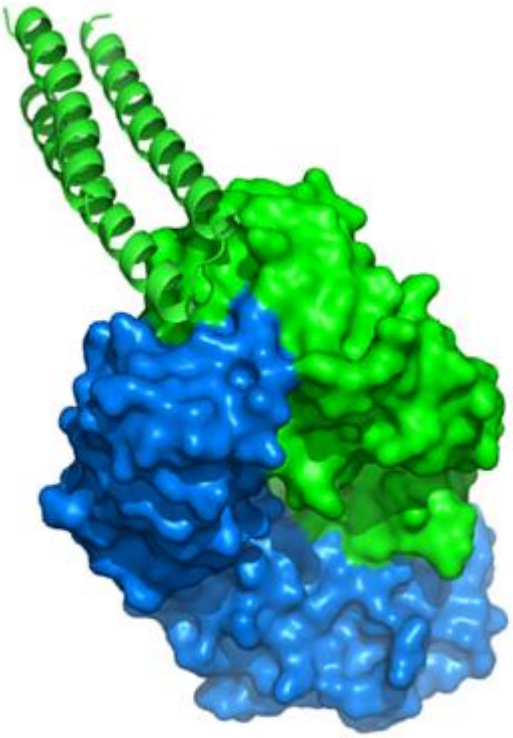

Image provided by Dr. Roland Strong.

Structure of a second-generation epitope-containing protein scaffold (green helices) bound by the RSV-directed antibody motavizumab (green and blue globule).