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A surrogate scaffold tested

Researchers tested an alternate antibody scaffold, creating so-called Surrobodies.

Besides their crucial role as one of our main defenses against disease, antibodies have also become an invaluable tool for basic research and have recently come full circle in an engineered form, used as therapeutics in the human body. "There is now significant interest in alternatives to classical antibodies," says Ramesh Bhatt of Sea Lane Biotechnologies, "and pre–B cell receptors seemed like an obvious therapeutic scaffold that had not been utilized." Pre–B cell receptors, produced by the immune system in the course of generating antibodies, contain two heavy chains, but instead of the light chains as in the mature antibody, they have two surrogate light chains (SLCs)—VpreB and λ5.

Bhatt and co-workers at Sea Lane created expression vectors and successfully expressed scaffolds containing these SLCs—named Surrobodies—in mammalian cells, in *Escherichia coli* and using phage display. As proof of concept, they constructed libraries using bone marrow of individuals who survived infection with the H5N1 influenza virus, with subsequent selection against the viral hemagglutinin protein. These libraries yielded several different Surrobodies capable of binding the antigen with high affinity.

"What we do know is that the method is general," says Richard Lerner of the Scripps Research Institute, also an author on the paper. The group proposes several ways to improve the affinity of the Surrobodies—by engineering diversity into the SLC loops.

What differentiates the Surrobody scaffold from mature antibodies are two tails on the SLCs: a 50-amino-acid N-terminal extension in λ5 and a 21-residue C-terminal tail in VpreB. "These tails allow building in new function or enhancing function of what one would expect with a normal antibody," explains Bhatt. Not only do these extensions provide extra antigen-recognition surface, the authors suggest manipulating them to improve antigen recognition or replacing them with peptides that will confer new function—such as targeting signals. Moreover, protease-binding sites could be engineered to remove these extensions when necessary.

"We're aggressively pursuing this new scaffold for therapeutic utility," says Bhatt. And no doubt others will grab these molecules by their tails as well.

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Xu, L. *et al.* Combinatorial surrobody libraries. *Proc. Natl. Acad. Sci. USA* **105**, 10756–10761 (2008).