Binders from the deepest vaults

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Vaughan et al. describe the construction of a very large library (1.4 x 10^{10} clones) of human single chain Fv (scFv) fragments displayed on the surface of filamentous phage[1] on p.309 of this issue. The library was used to isolate very rapidly (less than two weeks, compared to four weeks for some other libraries) monoclonal scFv against several different proteins including self-antigens and haptens. The tightest binding antibodies have dissociation constants (K_d) in the subnanomolar range and a higher affinity than previously isolated from a naive (nonimmunized) library, comparable to the best hybridoma-derived antibodies. The rapidity of deriving antibodies from large phage libraries gives this technology the potential to accelerate many areas of biomedical research and supersede hybridomas as the preferred method of producing reagent antibodies. Antibodies derived from (or manipulated using) phage libraries also have the promise to dominate the next generation of therapeutic antibodies.

The advent of antibody phage in 1990[2] was followed by rapid evolution in corresponding libraries[3,4]. The first naive human scFv library yielded small numbers of micromolar affinity antibodies against target antigens[5]. This encouraged the development of a very large (6.5 x 10^{10} clones) semisynthetic library in Fab format, which yielded larger panels of antibodies against diverse targets with K_d values in the nanomolar range[6]. The very large library of Vaughan et al.[1] extends large antibody library technology by demonstrating the utility of the alternative scFv format, by showing that subnanomolar affinity antibodies can be obtained and by avoiding the need to subclone in order to characterize identified antibodies.

Antibodies derived from large phage libraries are likely to be used directly as research reagents. For therapeutic applications, it is feasible, desirable, and perhaps necessary to optimize rapidly the antibody fragment. Again, phage systems can be used. For example, in some cases it may be desirable to increase the affinity of antibody fragments from the nanomolar to picomolar range by random mutagenesis of antigen binding loops, as demonstrated for an anti-gp120 antibody[7]. Some scFv fragments identified by Vaughan et al. contain multiple changes from the germline V gene sequences, probably reflecting both somatic and PCR-generated mutations. Removing such mutations (as far as possible while preserving antigen binding) may minimize the potential risk of immunogenicity of the corresponding antibody in patients. It may sometimes be possible to select for antibodies that bind both a human antigen and the corresponding molecule from some animal species. This would permit preclinical and clinical studies to be conducted with the same antibody, thereby streamlining the drug development process. In addition, the antigen-binding variable domains of the scFv might be recast into one of numerous possible alternative formats [for instance, Fab, F(ab′)2 IgG, minibody, diabody, and miniantibody] to tailor the pharmacokinetic or pharmacodynamic properties or to recruit desired effector functions.

This technology has the potential to accelerate many areas of biomedical research and supersede hybridomas as the preferred method of producing reagent antibodies.

Widespread adoption of large antibody phage libraries by those developing therapeutic antibody moieties will require, first, that they are robust and easy to use, and second, that they are readily available. The Vaughan et al. library is robust and easy to use, as judged from my laboratory's experience: We have identified more than 100 antibodies against 8 different proteins, including receptor antagonists and agonists, as well as against proteins that are highly conserved between species. It will be down to market forces to make sure the libraries are available.

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