MOLECULAR BIOLOGY

Bespoke antibodies fast tracked

A yeast cell culture approach mimics the benefits of somatic hypermutation to accelerate the discovery of desirable antibodies.

For decades, antibodies have been a pillar of countless research projects.

Yet generation of antibodies with the desired characteristics remains difficult. The process is slow, problematic to scale and often requires immunization of animals, this last associated with its own challenges, including the ethics of animal husbandry. Researchers led by Andrew Kruse from Harvard Medical School in Boston and Chang Liu from the University of California in Irvine have developed a faster, affordable and perhaps more reliable path to a custom antibody.

The approach, called AHEAD for “autonomous hypermutation yeast surface display”, combines orthogonal DNA replication, yeast surface display and fluorescence-activated cell sorting. During yeast culture growth, an orthogonal error-prone DNA polymerase introduces

mutations in a plasmid that encodes antibodies (or antibody fragments), resulting in a mutation rate that is 100,000-fold higher than the genomic mutation rate in yeast. The antibodies encoded on the plasmid are expressed as fusion proteins to ensure surface display, and cells are subjected to sequential rounds of diversification and sorting for desired antigen binding. The simplicity of the approach enables parallel evolution of several early clones, which results in selection of high-affinity, high-quality antibody clones in a short period of time: one of the reported examples produced improved antibodies in only three days.

Kruse, Liu and colleagues showcased the potential of the system by generating high-affinity nanobodies against the receptor-binding domain of the SARS-CoV-2 spike protein. These nanobodies,

when fused to the Fc region of the human immunoglobulin G1, were able to potently neutralize the virus. Finally, the researchers demonstrated that AHEAD can encode entire naïve antibody libraries for generation of antibodies against new targets.

“We envision a future where any lab can evolve potent antibodies against any antigen just by growing yeast,” says Liu. AHEAD is a step towards that goal.

Katarzyna Marcinkiewicz

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 Wellner, A. et al. Rapid generation of potent antibodies by autonomous hypermutation in yeast. *Nat. Chem. Biol.* <https://doi.org/10.1038/s41589-021-00832-4> (2021).

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