

Vaccinex Inc.

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Perfecting *in vitro* mammalian display for antibody selection

Vaccinex's proprietary full-length human antibody discovery engine, ActivMAB, integrates selection and manufacturing in the same mammalian host to streamline development.

Antibodies as therapeutics have dominated the clinical landscape over the past 15 years because of their selective targeting, increased drug safety and fewer side effects. Traditional antibody drug discovery platforms based on *in vitro* selection use surrogate production hosts such as bacteria and yeast. However, antibodies expressed in these cells do not undergo the post-translational quality control that occurs in mammalian cells, and this can lead to unpredictable expression or undesirable biophysical properties that may present major challenges during production and development.

To overcome these challenges, the privately held clinical-stage biotech company Vaccinex has developed a proprietary platform called ActivMAB for rapid, mammalian cell-based antibody selection. The platform achieves throughput comparable to phage and yeast display; it also provides mammalian cell quality control for the efficient selection of full-length human antibodies, built-in manufacturability and favorable biophysical properties ideally suited for downstream development. Vaccinex is using the platform to both build its own antibody pipeline and provide services to biopharmaceutical partners.

"We have developed one of only a handful of major commercial platforms for human antibody discovery," said Mark Paris, director of bioinformatics and molecular biology at Vaccinex. "Our platform produces better antibodies because it requires efficient and stable mammalian cell expression for selection. Moreover, their solubility, expression and biophysical characteristics make them ideal for downstream applications."

Built for success

At the core of Vaccinex's technology is the ability to efficiently construct large and diverse libraries of recombinant vaccinia virus containing complementary DNAs (cDNAs) of interest. This virus is an ideal vehicle because it is capable of robust expression and infects most mammalian cells. Vaccinex engineers a fusion between the complete immunoglobulin heavy chain and an integral vaccinia virus membrane protein to enable expression of the antibody on the surface of the virus as it is shed from the cell (Fig. 1). Concurrently, the antibody is expressed on the surface of infected cells.

The technology couples the panning of viral particles with the sorting of infected cells, enabling the efficient identification of high-affinity, fully human antibodies from antibody libraries expressed in mammalian cells. The



Figure 1: Vaccinex's mammalian cell-based antibody discovery platform. Recombinant vaccinia virus particles contain large and diverse libraries of heavy- and light-chain genes for the display of full-length human antibodies. After infection of mammalian cells, the shed virus displays antibody on its surface (depicted) and simultaneously on the surface of the infected cell.

initial stage of panning antibody-expressing viral particles on antigen-coated magnetic beads allows rapid screening of billions of antibody combinations—a process that would not be feasible with sorting of mammalian cells, owing to their relatively large size.

In the subsequent cell-sorting stage, which can be performed immediately without re-engineering, infected mammalian cells are incubated with fluorescently labeled antigen, and those expressing antibodies that bind antigen are separated by fluorescence-activated cell sorting (FACS). This process enables the tunable selection of antibodies on the basis of expression and affinity to antigens of interest. "FACS sorting is a powerful final step to the process that allows for tunable selection and the introduction of cross-species sorting or negative selection," Paris said.

Multipurpose platform

In addition to its utility for *de novo* antibody selection, the technology platform can be used to convert mouse antibodies to fully human antibodies, improve the affinity of antibody candidates and investigate an antibody's mechanism of action. Many new discovery projects begin with a mouse monoclonal antibody that has properties desired in a fully human therapeutic. Vaccinex has developed efficient strategies to quickly convert mouse antibodies to fully human antibodies while preserving specificity and function.

For its antibody improvement strategies, the company leverages the modular nature of its heavy- and light-chain libraries. Because they are created separately, these libraries enable researchers to quickly find improved chains by keeping one chain constant during screening. This strategy can lead to the selection of antibodies with higher affinity than antibodies created from other processes. The technology is also amenable to screening against multiple species and/or depleting candidate antibodies that bind to homologs. Furthermore, the modular nature of the libraries allows for the identification of light chains that are common to antibodies to two or more antigens for the assembly of bispecific antibodies.

Vaccinex has also implemented assays in its discovery process that prioritize candidate antibodies according to production levels, thermostability, solubility and stability (i.e., percentage monomer). Moreover, Vaccinex is fully equipped to implement custom *in vitro* functional assays.

Pipeline and partnerships

Vaccinex has used its platform for the discovery and development of human therapeutic monoclonal antibodies to treat serious diseases with unmet needs, including cancer and multiple sclerosis. The company's antibody to semaphorin 4D, VX15, has been through two successfully completed phase 1 clinical trials in patients with either advanced solid tumors or multiple sclerosis.

Beyond using its platform to build its own pipeline, Vaccinex is actively seeking partnerships with companies that aspire to develop antibody therapeutics. Earlier this year, the company entered into a multitarget collaboration agreement with Five Prime Therapeutics to use ActivMAB for the discovery of monoclonal antibodies to new targets from Five Prime's proprietary discovery platform.

"Innovation has long been the driving force in value creation for biotech companies," said Maurice Zauderer, president and CEO of Vaccinex. "We look forward to novel products emerging from our ActivMAB discovery platform, both internally and through collaboration with our valued partners."

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