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ABLEXIS

HARNESSING PLATFORM TECHNOLOGY AND EXPERTISE FOR ANTIBODY DISCOVERY

A conversation with **LARRY GREEN**, **PhD**, chief executive officer of Ablexis and AlivaMab Discovery Services

The demand for safe therapeutic monoclonal antibody (mAb) candidates with more complex target product profiles is driving a need for more robust discovery platforms. In June 2018, Deerfield Management and Ablexis, which licenses the AlivaMab Mouse platform for the discovery of human therapeutic antibody candidates, founded AlivaMab Discovery Services, an organisation that provides antibody drug discovery services to industry and academia using the AlivaMab Mouse platform. Larry Green discusses how Ablexis and AlivaMab Discovery Services help clients accelerate the discovery of therapeutic mAbs best positioned to meet demanding target product profiles through discovery and development processes.

What are the main challenges in pre-clinical discovery and development of mAbs?
Decisions made in the discovery phase can have significant consequences later in development. In therapeutic discovery, there are many potential pitfalls, some of which may not become evident until tens, or even hundreds, of millions of dollars have been spent. The choice of discovery platform contributes more to the foundation of success than is realized.

Of course, understanding the biology of the target and its links to disease is paramount. The more that is known about the desired mechanism of action, the mechanism of efficacy, the required affinity of the antibody for the target and the necessary potency of activity for a therapeutic effect, the higher the chances of identifying the best leads.

It is also necessary to ensure that the antibody meets the requirements that are needed to be a drug, and ideally, to be best in its class. Does it have the necessary level of activity in vivo? Can it be manufactured in sufficient amounts to be commercially viable? Can it be formulated to high concentrations and be stable? Is it specific for its target, with no unforeseen off-target binding when administered to patients?

Does it have a reduced chance of eliciting anti-drug antibodies?

What are the options for producing fully human mAbs?
Broadly, fully human mAbs are typically discovered using transgenic animals that have been genetically engineered to make antibodies with human variable regions, or in vitro display technologies that rely on bacteriophage, yeast, or mammalian cells displaying human antibody proteins. At present, there are twice as many approved antibody drugs on the market from transgenic mice than from in vitro display technologies.

What are the key differences between in vitro display platforms and transgenic animals?
The biggest difference is that any good transgenic animal platform harnesses the animal's immune system to make antibodies with human variable regions. These antibodies have an incredible diversity, high affinity for binding to the target, high functional potency and intrinsic drug-like properties. In vitro display platforms attempt to mimic in plastic containers what the mammalian immune system has fine-tuned over millions of years of evolution. Although

these platforms offer a (sometimes) quick and a (sometimes) cheap solution to meet initial discovery goals, you are more likely to encounter problems further into the development process as antibody expression in vitro, whether it be on a bacteriophage, a yeast or an isolated mammalian cell, fails to reproduce the natural screening and selection checkpoints of the mammalian immune system.

What are the advantages of AlivaMab Mouse technology?
The AlivaMab Mouse was designed and built on 20+ years of experience in antibody drug discovery and development. The AlivaMab Mouse is the only transgenic animal with fully synthetic, autonomously functioning immunoglobulin transgenes. The DNA sequence of the immunoglobulin chains was designed down to the single nucleotide level, providing unique and unprecedented control over the function of the transgenes. The design and composition (part mouse/part human) of the synthetic transgenes is different from any other transgenic platform and supports the generation of robust and molecularly diverse immune responses, which yield panels of antibodies with epitope

diversity and high affinity that better support efficiency and risk-reduced pre-clinical and clinical development.

How can companies access the AlivaMab Mouse technology?
The AlivaMab Mouse is available for licensing; the platform is currently licensed to eight of the top 15 pharmaceutical companies, as well as to several other public and private companies, which are using the platform in-house. However, some companies would rather outsource their antibody discovery work. This is where the AlivaMab Discovery Services team comes into play.

What does AlivaMab Discovery Services offer these companies?
AlivaMab Discovery Services is dedicated to generating, recovering, and characterizing therapeutic antibody candidates from the AlivaMab Mouse platform. Our research team is led by people with vast experience in generating therapeutic-quality mAbs. We can help with project design and, working in collaboration with our clients, we aid in delivering novel solutions.