Three-species platform optimizes the discovery of diverse fully human antibodies

Ligand Pharmaceuticals’ cutting-edge OmniAb antibody platform leverages genetically engineered rats, mice and chickens to provide the industry’s widest epitope coverage with broad freedom to operate.

Human therapeutic antibodies constitute the industry’s fastest-growing therapeutic class. In the US, more than 500 antibodies are in various stages of clinical development, and the number of therapeutic antibody candidates in phase 3 clinical development now exceeds 50, a twofold increase over the past five years. By 2020, 10 of the top 20 pharmaceutical products are expected to be antibodies, accounting for more than 50% of sales. But the discovery of therapeutic antibodies has been limited by the relatively low diversity of antibody platforms.

To overcome this problem, Ligand Pharmaceuticals offers an innovative antibody platform called OmniAb, which combines several species and genetic backgrounds to increase the probability of success of antibody discovery. This transgenic-animal platform consists of four different technologies—OmniRat, OmniChicken, OmniMouse and OmniFlic—used for producing monospecific and bispecific human therapeutic antibodies in multiple species (Fig. 1). The patented technology offers broad freedom to operate and delivers fully human antibodies with high affinity, specificity, expression, solubility and stability.

The single-license OmniAb, which encompasses genetically engineered rats, mice and chickens, is the industry’s only antibody platform with three species and multiple genetic backgrounds. As a result, OmniAb provides the widest epitope coverage and can address even the most challenging targets, such as ion channels and G protein-coupled receptors (Fig. 2). The platform produces highly diversified, fully human antibody repertoires optimized in vivo for manufacturability, therapeutic efficacy and reduced immunogenicity.

“Ligand’s objective is to make OmniAb available to biopharmaceutical companies and academic institutions and help facilitate the continued market growth of therapeutic antibodies worldwide,” said Ligand’s president and COO, Matt Foehr.

Antibody advantages

Antibodies offer several favorable characteristics such as high specificity, minimal off-target effects and good safety profiles. By triggering several immune effector mechanisms, antibodies can effectively neutralize pathogens, inactivate target antigens or destroy malignant cells. In addition, because antibody manufacturing follows a similar process regardless of the intended drug target, the costs and risks of development are lower than with new small-molecule drugs.

Given these advantages, it is perhaps not surprising that antibodies have proved enormously successful both medically and commercially. The success rate for antibody classes is nearly twice the rate for small molecules. In 2016, the total therapeutic antibody market reached $81 billion according to BCC Research. The predominant portion of this came from current OmniAb partners such as Roche/Genentech, Janssen and AbbVie. BCC Research expects the market to grow to $115 billion by 2022, while others provide even higher estimates.

Although a few therapeutic antibodies on the market were identified using in vitro techniques, the vast majority of approved monoclonal antibodies were generated using mice. It’s well established that antibodies from phage libraries often run into problems with stability, aggregation and other manufacturability challenges. According to The Antibody Society, 77 therapeutic antibodies were approved or are pending approval in the US and Europe. More than 70 of these were generated in vivo by animals, but only a few were produced by phage-display technologies.

Immunization of rodents leverages complex immune processes, notably repertoire selection and antibody affinity maturation that cannot be recreated completely in vitro. However, to avoid triggering a harmful immune reaction in human patients, nonhuman immunoglobulin sequences must be eliminated from rodent and chicken-derived antibodies. This can be accomplished through humanization of antibodies produced from endogenous rodent or chicken immunoglobulin genes.

It is less time consuming and less risky to immunize transgenic animals bearing human immunoglobulin sequences. The most successful antibody discovery platforms are animal-based technologies that yield fully human antibodies. Therefore, older technologies such as murine, chimeric and humanized antibodies are now being replaced by fully human antibodies isolated from mice, rats and chickens.

Various transgenic mice expressing human antibodies have been developed using embryonic stem cell technology. But the methods developed in mice proved unworkable in rats, initially limiting commercial antibody discovery to a few transgenic mouse models. The OmniAb platform is based on groundbreaking work in gene editing to overcome this problem. To engineer the chicken immunoglobulin loci, scientists at Ligand developed the unique primordial germ cell platform that enables precise replacement of the endogenous genes with their human counterparts. The primordial germ cell technology was published in Nature in 2006 and its application in the creation of OmniChickens is described in the Proceedings of the National Academy of Sciences of the USA, and the European Journal of Immunology and mAbs.

Fig. 1 | OmniAb. This platform consists of four different technologies—OmniRat, OmniChicken, OmniMouse and OmniFlic—able to produce monospecific and bispecific human therapeutic antibodies.
Versatile platform maximizes success

In recent years, scientists created rats and chickens that express diversified repertoires of antibodies with fully human idotypes. These systems, known as OmniRat and OmniChicken, were developed, validated and commercialized by Ovaclone Biologics Inc. (OMT) and Crystal BioSciences Inc., respectively, and these companies were acquired by Ligand in 2016 and 2017. OMT also used the same antibody platform to generate OmniMouse and OmniFlic. The OmniChicken platform comes in several options including a lambda light-chain, kappa light-chain and two heavy-chain options.

OmniRat and OmniFlic are the only rats available for the generation of monospecific and bispecific human antibodies. In these systems, endogenous expression of rat immunoglobulin genes was inactivated using transient expression and two heavy-chain options. The subsequent insertion of recombinant immunoglobulin loci resulted in animals that express a diverse antibody repertoire and generate antibodies with human idotypes as effectively as wild-type animals produce rat and chicken antibodies. Both OmniChickens and OmniRats contain functional human recombinant immunoglobulin loci that range and generate functional fully human antibodies. In addition, both OmniChickens and OmniRats display normal B-cell development, high expression of immunoglobulins, V(D)J recombination, gene conversion (in OmniChickens), somatic hypermutation and affinity maturation.

OmniFlic is an engineered rat with the same heavy-chain transgene as OmniRat and a fixed light chain for the development of bispecific, fully human antibodies. Antibodies from OmniFlic comprise a single germline Vk sequence and can be generated through comprehensive analysis of the heavy-chain repertoires without any use of hybridoma technology.

OmniMouse and OmniChicken provide complementary murine and avian systems for the industry’s widest epitope coverage. For many target indications and antigens, mouse models are encumbered by existing intellectual property, and ongoing litigation presents a considerable risk. By contrast, OmniMouse and OmniChicken have complete freedom to operate and can be used to generate antibodies specific for any target and indication globally. OmniMouse expands the epitope coverage of OmniRat and creates the potential for even broader antibody discovery of single antibodies or antibody cocktails. OmniChicken yields many monoclonal antibodies (mAbs) that recognize both the human and murine antigen and therefore obviates the use of surrogate antibodies in preclinical studies. In many campaigns, OmniChickens have yielded mAbs that recognize the human, cynomolgus monkey, rat and murine orthologs. This feature, which is a consequence of the large phylogenetic distance between birds and mammals, has led to broad application by Ligand’s partners.

Because each individual animal mounts a different antibody response following immunization with a target antigen, the availability of all three species is a key platform advantage that ensures drug discovery of the greatest probability of success.

Partners expanding the OmniAb pipelines

Ligand has assembled the largest and most diverse portfolio of antibody discovery platforms in the biotech and pharmaceutical industry. Ligand has leveraged its groundbreaking science to form multiple alliances, many licenses and broad business relationships with the world’s leading pharmaceutical companies. To date, more than 30 biopharmaceutical companies and several universities have established unlimited OmniAb access. OmniAb antibodies have been generated against more than 300 targets, and 7 are now in clinical development, with many more expected. The OmniAb business continues to expand, driven by industry demand for leading antibody discovery technologies with multiple species and broad freedom to operate.

Recently, Ligand announced that it has entered into a worldwide OmniAb platform license agreement with Ferring Pharmaceuticals and Glenmark Pharmaceuticals. A couple of months later, Ligand announced that it entered into an agreement with venBio Partners, a venture capital group focused on building and funding portfolio companies with first and best-in-class therapeutic product applications. Under these agreements, Ferring, Glenmark and venBio’s portfolio companies will be able to use the OmniAb mice, rats and chickens to discover fully human monospecific and bispecific antibodies.

“The deal with venBio Partners represents an OmniAb first in terms of enabling a venture investor to incubate a series of new companies with common OmniAb licensing terms, enabling their portfolio companies to focus on drug development and value creation from the start,” said Foehr.

In June 2018, Ligand announced that it received $47 million as a result of signing an amendment relating to its OmniAb platform agreement with WuXi Biologics. This amendment provides WuXi Bio more efficiency to expand its OmniAb antibody discovery services. With this new business relationship, WuXi Bio believes it will be able to increase the number of its OmniAb antibody discoveries for its clients in China and around the world.

“The expanded agreement with WuXi Bio demonstrates the continued success of our OmniAb platform, and illustrates the focus and ongoing efforts by OmniAb partners to advance their OmniAb pipelines,” said Foehr. “This transaction also underscores the significant value a key partner sees in the OmniAb platform, and we are pleased to offer WuXi Bio this added flexibility as they discover antibodies with our platform.”

OmniRats, OmniMice and OmniChickens are offered with flexible terms for all targets, indications and territories through unlimited licenses. Moreover, OmniAb antibody discovery services are available from Ligand-approved contract research organizations in the US, Europe and Asia. These services may offer the most cost-efficient way to generate and characterize therapeutic OmniAb antibodies. In the case of rodents, OmniAb licensees may also procure animals directly from the breeders and conduct the antibody discovery internally. OmniChicken antibody discovery campaigns are conducted by Ligand’s dedicated OmniChicken facility.

By 2025, the platform is expected to generate more than 40 clinical-stage programs and more than 150 research-stage candidates through an estimated 60 partnerships. “Our OmniAb antibody discovery business is thriving as we continue to sign up new partners. There is significant demand for research tools to facilitate drug discovery, and our novel platform of transgenic animals, proprietary assays and intellectual property make our offering a very attractive package for licensing,” Foehr said. “We continue to invest in the platform and secure more deals that will drive Ligand’s future growth.”