Open Monoclonal Technology, Inc.

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OmniRat™ technology produces "naturally optimized human antibodies™"

OmniRat produces antibodies with human idiotypes as efficiently as wild-type animals produce rat antibodies. The technology offers unrestricted development opportunities across targets and indications.

With a noval genetic engineering approach, Open Monoclonal Technology (OMT) has created the OmniRat platform that provides a new way of producing monoclonal antibodies (mAbs) using transgenic rats. Until now, mouse-based technologies were the only commercially available animal-based platforms for generating human mAbs, but as expenses and intellectual property constraints grew, OMT founder and CEO Roland Buelow saw the opportunity for a new approach.

Buelow has over 25 years of biotechnological research experience and previously founded Therapeutic Human Polyclonals, which engineered rabbits to produce human antibodies. That company was acquired by Roche in 2007. The subsequent acquisition of Abgenix by Amgen and Medarex by Bristol-Myers Squibb severely restricted access to animal-based human antibody platforms and persuaded Buelow of the potential demand for alternatives.

In 2008, Essex Woodlands Health Ventures came on board with the financial backing that enabled OMT to complete the platform within just three years. With unrestricted development opportunities across targets and indications and the ability to generate highly specific, fully human antibodies of desired affinity and manufacturability, OmniRat is an attractive alternative technology that could save drug development companies significant time and costs.

The company works virtually with all development outsourced to expert service providers or carried out by collaborators with proven track records. Essential to the successful development of OmniRat was OMT collaborator Marianne Brüggemann and her team, formerly of the Babraham Institute and now of Recombinant Antibody Technology. Additional expertise was provided by a scientific advisory board including Michael Neuberger at the Medical Research Council Laboratory in Cambridge, UK; C. Geoffrey Davis, president and CEO of Angelica Therapeutics and former CSO of Abgenix; and Ignacio Anegon, director of INSERM.

Developing the OmniRat platform posed some significant challenges. OMT needed to make two strategic innovations—inactivate the rat's own immunoglobulin genes and eliminate suboptimal signaling by the B cell receptor complex that occurred in earlier mouse systems. These advances enabled OmniRat to express human antibodies as effectively as normal rats express their own antibodies.

"Creating an immunoglobulin knockout rat was the biggest challenge we faced," said Buelow. "Previous platforms used either embryonic stem cells or nuclear transfer cloning techniques that were not available for the genetic engineering of rats. Instead we explored a new application for zinc finger nuclease (ZFN) technology."

ZFNs are engineered proteins that induce double-strand breaks at specific sites in an organism's DNA. Such double-strand breaks stimulate the cell's own DNA-repair pathways, resulting in frequent DNA sequence changes. OMT used ZFNs developed by Sangamo BioSciences to disrupt rat immunoglobulin genes. This major breakthrough was the first example of permanent, heritable, targeted gene silencing in rats and was published in *Science* in 2009. OMT has a ZFN license from Sangamo BioSciences for the exclusive commercial use of immunoglobulin knockout rats in which no endogenous heavy and light chains (both kappa and lambda) are being produced.

The second challenge of eliminating the suboptimal signaling by the B cell receptor complex was met in collaboration with Brüggemann and scientists at Recombinant Antibody Technology. They used artificial chromosome technology to generate hybrid immunoglobulin loci encoding antibodies with human idiotypes and rat constant regions. This resulted in extensive rearrangement and diverse expression of the human variable region combined with high levels, class switching and hypermutation provided by the rat constant region portion of the IgH locus.

The final step of cross-breeding the knockout animals with rats expressing human antibodies was completed in 2010. The resulting OmniRat platform offers a unique method for generating fully human antibodies without a need for further optimization of lead candidates. OmniRat also eliminates the task of humanization of animal-derived antibodies or lead optimization of display candidates. OMT refers to this advance as "naturally optimized human antibodies™."

The major advantage of the platform is the unrestricted development options across all targets and indications. OMT will keep access to the platform open and is not looking for target-exclusive deals, a sentiment indicated in the use of 'omni' in the platform's name. Brian Lundstrom, OMT chief business officer, said, "We are seeking widespread use of OmniRat, from the largest pharmaceutical companies via biotechs and small startups to academics."

OMT's offers access to the platform in several ways. On September 18, OMT announced an agreement with Pfizer. Buelow explained, "Pfizer has had access to the platform for eighteen months and generated antibodies against a series of targets. Several of these antibodies had sub-nano-molar affinity and in some cases OmniRat deliver antibodies where murine systems did not. The collaboration represents the first time an OMT partner gets unlimited, royalty-free access to OmniRat for all targets and indications. OMT is set up to offer similar access to a limited number of partners."

OMT also grants single- and multitarget licenses with milestones, royalties or sublicensing fees. In July, OMT entered into such a deal with Merck KGaA whereby OMT will use OmniRat to generate antibodies against several targets and Merck will have the right to develop and commercialize these as therapeutic products.

In September, OMT announced a partnership with WuXi AppTec to jointly develop human antibodies against a number of therapeutic targets. This alliance combines the companies' human antibody and integrated development capabilities to generate therapeutic leads for licensing by pharmaceutical companies globally. It illustrates OMT's ability to participate in risk-and profit-sharing programs with competent partners.

While OMT implements its business strategy for OmniRat, the company is also developing an OmniMouse™ platform. Buelow explained that multiple animal platforms will provide greater opportunities for finding effective mAb therapies because each species creates antibodies with unique specificities. "With more animal options we can cover more epitopes. With OmniMouse, OMT will offer a one-stop shop for companies looking for naturally optimized therapeutic human antibodies."

OmniRat
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CONTACT DETAILS

Brian Lundstrom
Open Monoclonal Technology,
Palo Alto, California,
USA
Tel: + 1-510-220-5599