DEAL WATCH

Ablynx and Merck Serono collaborate on next-generation antibody products

Ablynx and Merck Serono have entered into an agreement to co-discover and co-develop nanobodies — a class of antibody-derived therapeutic proteins — against two unspecified targets in oncology and immunology. Under the agreement, Ablynx receives an upfront cash payment of 10 million euros, and the companies will equally share all R&D costs. Total development and commercial milestones, depending on if and when Ablynx exercises options for partly or fully opting out of the partnership, could reach up to 325 million euros.

This agreement follows several similar collaborative deals/acquisitions involving large pharma companies and companies developing next-generation antibody derivatives (TABLE 1), reflecting the growing interest in alternatives to monoclonal antibodies over the past decade (*Nature Biotech.* 23, 1126–1136; 2005). Several types of antibody fragments, as well as alternative scaffolds (*Nature Biotech.* 23, 1257–1268; 2005), are now in clinical trials and Genentech's ranibizumab (Lucentis) (*Nature Rev. Drug Discov.* 5, 815–816; 2006) provides a successful example of an antibody fragment that has already received FDA approval.

Nanobodies harness the structural and functional properties of antibodies from camelids, which contain a single variable domain, and are small enough to penetrate cavities in target proteins, such as enzyme active sites. Several other analogous technologies being pursued are highlighted in TABLE 1.

The growing popularity of these technologies stems from the advantages compared with full-size antibodies. "They can easily be selected or engineered for highly specific binding to a target antigen, while retaining the inherent stability and solubility associated with immunoglobulin domains," says Mike Clark, University of Cambridge, UK, who has been working on therapeutic antibody technologies for more than two decades.

"Owing to their small size, they are also more easily produced than traditional antibodies, in a range of different expression systems, including bacteria and yeast," he adds. This could reduce manufacturing costs compared with traditional antibodies, which are often produced in mammalian expression systems. The fragments can also be engineered into more complicated products, such as bi- or tri-specific complexes, or modified to increase their half-life, which is typically much shorter than traditional antibodies.

Immunogenicity issues with next-generation antibody-like products represent a potential major challenge, although Clark thinks that the wealth of experience with antibody-based therapies in general will help address this. These products also lack an inherent effector function, which might be important in some diseases. Nevertheless, "since the desirable properties of antibodies vary according to disease, having multiple tools in your toolbox is what it is all about," concludes Clark.

Table 1 | **Selected novel antibody fragment technologies in development***

Molecule/scaffold	Company	Target antigen	Indication
Nanobodies/heavy-chain camelid antibodies	Ablynx	vWF, TNF-α, other unspecified	Thrombosis, RA‡, IBD‡, oncology§, immune disorder§, AD‖
Domain antibodies/ heavy- or light-chain human antibodies	Domantis¶	TNF-α/TNF1R CD40, IL13/IL4, other unspecified	RA, Crohn's disease, COPD, autoimmune disease, asthma, oncology
Shark antibodies/ shark IgNAR	Haptogen#	Unspecified	Infectious diseases, oncology, inflammation
Unibodies/modified human IgG4	Genmab	Unspecified	Oncology, autoimmune/ inflammatory conditions

*All in preclinical stage except nanobodies (Phase Ib). ‡Collaborative deal with Wyeth. §Collaborative deal with Merck Serono. ‖Collaborative deal with Boehringer Ingelheim. ¶Acquired by GlaxoSmithKline, Dec 2006. #Acquired by Wyeth, Oct 2007. AD, Alzheimer's disease; COPD, chronic obstructive pulmonary disease; IBD, inflammatory bowel disease; IgNAR, immunoglobulin isotype novel antigen receptor; IL, interleukin; RA, rheumatoid arthritis; TNF-α, tumour-necrosis factor-α; TNFR1, tumour-necrosis factor receptor 1; vWF, von Willebrand factor.