BIOBUSINESS BRIEFS

DEAL WATCH

BMS acquires rights for IL-6 inhibitor

Bristol–Myers Squibb (BMS) has entered a potential ~US$1 billion agreement with Alder Biopharmaceuticals involving Alder's lead drug ALD518, a humanized monoclonal antibody specific for interleukin-6 (IL-6) that has successfully completed a Phase IIa trial for rheumatoid arthritis.

Through the deal, which involves an upfront payment of $85 million and almost $1 billion in possible milestone payments, BMS gains exclusive worldwide development rights for all indications apart from cancer, which are retained by Alder. A Phase IIb trial of ALD518 in rheumatoid arthritis is under way, and Alder is also working on a new subcutaneous formulation of the antibody, which is produced using a novel yeast-based expression system.

"IL-6 plays a central role in inflammatory diseases together with other inflammatory cytokines such as TNF [tumour necrosis factor] and IL-1," explains Norihiro Nishimoto, Professor in the Laboratory of Immune Regulation at the Wakayama Medical University, Wakayama, Japan. "Antibodies developed against the IL-6 receptor have shown to be therapeutically effective in patients with rheumatoid arthritis, systemic juvenile idiopathic arthritis, Castleman's disease and Crohn's disease that are refractory to conventional therapies such as corticosteroids and other disease-modifying antirheumatic drugs." (*Nature Clin. Pract. Rheumatol.* **2**, 619–626; 2006).

Indeed, an injectable humanized monoclonal antibody specific for the IL-6 receptor, tocilizumab (Actemra/RoActemra; Chugai/Roche), was launched in Japan in 2005, initially for Castleman's disease. It was subsequently also approved for rheumatoid arthritis both in Japan and the European Union, on the basis of trials demonstrating efficacy in patients who had responded inadequately to, or were intolerant to, other disease-modifying antirheumatic drugs, including the widely used TNF antagonists (*Nature Rev. Drug Discov.* **8**, 273–274; 2009).

The validation of IL-6 as a target for autoimmune diseases such as rheumatoid arthritis has provided the impetus for the development of second-generation IL-6 inhibitors or fast follow-ups by other pharmaceutical companies. Regeneron is working on a fully human antibody against the IL-6 receptor, whereas Centocor and Alder have been focusing on generating antibodies against IL-6 itself (TABLE 1).

"Theoretically, IL-6 production differs among patients, whereas IL-6 receptor production is almost consistent among individuals; therefore, it might be easier to target the receptor. However, blocking the ligand seems more straightforward than blocking the IL-6 receptor, and so it is not easy to say which strategy is better," comments Nishimoto.

Iain McInnes, Professor of Experimental Medicine and Rheumatology, University of Glasgow, agrees. "The benefits of targeting IL-6 directly rather than the receptor remain unclear but, given the *cis* and *trans* signalling activities of IL-6 (mediated by the membrane-anchored and soluble form of the receptor, respectively), it is possible that the responses using these two strategies to block IL-6 may diverge in time. Careful perusal of forthcoming clinical trial data will be required," he concludes.

Table 1 | **Selected antibodies in development targeting IL-6 or its receptor**

Drug (developer)	Properties	Selected indications (status)
Tocilizumab (Chugai/Roche)	Humanized mAb specific for the IL-6 receptor	Castleman's disease, rheumatoid arthritis and JIA (launched)
REGN-88 (Regeneron)	Fully human mAb specific for the IL-6 receptor	Rheumatoid arthritis (Phase I)
CNTO-136 (Centocor Ortho Biotech)	Fully human mAb specific for IL-6	Cutaneous lupus erythematosus, rheumatoid arthritis and SLE (Phase II)
CNTO-328 (Centocor Ortho Biotech)	Chimeric mAb specific for IL-6	Renal cell carcinoma, multiple myeloma and prostate tumour (Phase II)
CDP-6038 (UCB SA)	mAb specific for IL-6	Rheumatoid arthritis (Phase II)
ALD518 (Alder/Bristol–Myers Squibb)	Humanized mAb specific for IL-6	Rheumatoid arthritis, cachexia and fatigue (Phase II)

IL-6, interleukin-6; JIA, juvenile idiopathic arthritis; mAb, monoclonal antibody; SLE, systemic lupus erythematosus.