IN brief

Amgen fined $762 million

Associated Press

Amgen in December pleaded guilty to off-label promotion of its $2-billion anemia drug Aranesp (darbepoetin alpha) and was fined $150 million, as part of a broader $762-million settlement with the US government. The charge resolves a series of criminal and civil allegations of illegal marketing practices around several other drugs, including rheumatoid arthritis treatment Enbrel (etanercept). In what began as a whistleblower lawsuit by a former sales executive and evolved into a full-blown federal government investigation, the Thousand Oaks, California–based Amgen was accused of misbranding Aranesp in renal disease at higher, less frequent dosages than those approved by the US Food and Drug Administration (FDA), to gain market share from Johnson & Johnson's Procrit (epoetin alpha). Amgen was also charged with marketing Aranesp for unapproved use in chemotherapy-induced anemia, and with offering illegal kickbacks to doctors.

This was the latest in a string of drug firm settlements related to off-label promotion. Coming just days after a US appeals court decision to overturn sales rep Alfred Caronia's conviction for promoting off-label use of Dublin-based Jazz Pharmaceuticals' drug Xyrem (sodium oxybate) on the basis of his First Amendment right to free speech, the fine restoked the debate around what constitutes off-label promotion, and whether FDA rules in this regard are stifling commercial speech. As dissenting US Court of Appeals judge Debra Ann Livingston noted in court, "if drug manufacturers were allowed to promote FDA-approved drugs for non-approved uses, they would have little incentive to seek FDA approval for those uses." To date, apart from Caronia, FDA has struggled to stay within the boundaries of the First Amendment and issue criminal prosecutions for off-label promotions, notes John Engel, founding partner at Engel & Novitt in Washington, DC. FDA is reviewing its guidelines, including those on how to deal with physicians' unsolicited requests for off-label information. But "given the dictates of the First Amendment, it's very challenging to put down in black and white what's allowed and what's not," notes Engel. Chad Landmon, partner at Axinn, Veltrop Harkrider in Hartford, Connecticut, reckons the agency has already clamped down over the last few years and that any new guidelines "won't bring significant changes." *Melanie Senior*

Table 1 Selected co-receptor drug discovery & development deals

Company	Partner	Targets	Potential value	Date
BMS	Medarex	CTLA-4, PD-1	$2.4 billion[a]	7/28/2009
GlaxoSmithKline (GSK)	University of Texas MD Anderson Cancer Center	OX40	$335 million	12/7/2012
GSK	Amplimmune	PD-1	$508 million	8/4/2010
MedImmune	Cancer Research Institute; Ludwig Institute for Cancer Research	CTLA-4 OX40 PDL1 (programmed cell death ligand 1)	n/a	10/9/2012
MedImmune	AgonOx; Providence Cancer Center	OX40	n/a	10/31/2011
4-Antibody, Recepta BioPharma	Ludwig Institute for Cancer Research	n/a	n/a	1/29/2013

[a]Acquisition deal.

director of technology development at the LICR. "What we don't know ultimately is what will be the most effective [co-receptor] to target." The consortium has not fully characterized the targets it is working on. "We're trying to develop a fast follower program," says Burns. It has some deep-pocketed rivals for company (**Table 1**).

Bristol-Myers Squibb (BMS) has gained a leading position in the area through its $2.4-billion acquisition of antibody developer Medarex (*Nat. Biotechnol* **27**, 781–783, 2009). The FDA approval of Yervoy (ipilimumab), an inhibitor of the immune checkpoint cytotoxic T-lymphocyte antigen-4 (CTLA-4), for treating metastatic melanoma in 2011, was a key milestone in the development of cancer immunotherapy and has stimulated much of the activity that has followed (*Nat. Biotechnol.* **29**, 1083–1089, 2011). CTLA-4 normally competes with the stimulatory T-cell co-receptor CD28 for binding to their shared ligands, B7-1 (CD80) or B7-2 (CD86). Preventing CTLA-4 from binding to B7-1 or B7-2 removes its inhibitory block on T-cell activation and allows the immune system to mount a response to cancer. New York–based BMS reported sales of $706 million in 2012, the product's first full year on the market.

BMS and its partner, Osaka, Japan–based Ono, have also begun phase 3 trials, in several cancers, of another human monoclonal antibody immune checkpoint inhibitor, nivolumab (BMS-936588), which targets the PD-1 receptor, a protein that blocks T-cell activation at a later stage in the immune response than CTLA-4. BMS reported last year that the drug achieved durable responses in several advanced cancer indications (*Nat. Biotechnol.* **30**, 729–730, 2012).

Vijay Kuchroo identified the inhibitory co-receptor T-cell immunoglobulin-3 (Tim-3) more than a decade ago. The protein, which is expressed by interferon-gamma producing $CD4^+$ T-helper cells and $CD8^+$ cytotoxic T-lymphocytes, promotes T-cell death when it binds its ligand, galectin-9. Kuchroo and colleagues demonstrated in three preclinical models that hitting Tim-3 and PD-1 simultaneously elicited far more potent effects than did hitting either one singly (*J. Exp. Med.* **207**, 2187–2194; doi/10.1084/jem.20100643). CoStim and several big pharma firms have ongoing programs in this area. Similar effects are seen when another inhibitory co-receptor, lymphocyte activation gene 3 (LAG-3) is targeted along with PD-1. "They look the same, but I'm sure there are subtle differences," says Kuchroo. The two receptors share similar regulatory features. "Wherever you see Tim-3, you also see LAG-3, and they're regulated by the same transcription factor. They come together," Kuchroo says.

OX40 (also called CD13), a member of the tumor necrosis factor (TNF) receptor family, is expressed on the surface of activated $CD4^+$ T-helper cells and $CD8^+$ cytotoxic T-lymphocytes. Binding between OX40 and its ligand OX40L (CD252) boosts T-cell division and survival, resulting in stimulation of both immune effector and memory functions (*Annu. Rev. Immunol.* **28**, 57–78, 2010). During his tenure at Houston-based MD Anderson, Yong-Jun Liu (now director of the Baylor Institute for Immunology Research in Dallas) identified an additional role for OX40L—it shuts down immunosuppressive regulatory T-cells found in tumors (*Proc. Natl. Acad. USA* **103**, 13138–13143, 2006). The humanized anti-OX40 antibodies now in GSK's hands mimic this function, as well as the other co-stimulatory effects associated with OX40–OX40L binding. "We are not the first to target this antibody in cancer," says Liu, but adds that the antibodies his team has discovered "have better biology." The MedImmune division of London-based