DEAL WATCH

HGS and FivePrime in FGF 'ligand trap' deal

Human Genome Sciences (HGS) and FivePrime Therapeutics have entered into an agreement to develop and commercialize FP-1039, a fibroblast growth factor (FGF) ligand trap, for cancer indications. Under the terms of the agreement, which could be worth up to almost US$500 million for FivePrime Therapeutics, HGS has acquired the rights to develop and commercialize FP-1039 in the United States, Canada and Europe, whereas FivePrime Therapeutics retain development and commercialization rights in the rest of the world.

FP-1039 consists of the extracellular domain of FGF receptor 1c (FGFR1c) splice isoform, which is fused to the Fc (crystallizable fragment) region of human immunoglobulin G, with modifications to increase the stability of the fusion protein. FP-1039 acts to sequester FGF ligands, thereby preventing them from binding to and activating their cognate FGFRs.

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There are a total of 18 FGF ligands, most of which bind to more than one receptor. FP-1039 specifically targets an entire family of FGF ligands. As Nicolas Turner at the Institute of Cancer Research and the Royal Marsden Hospital, London, UK, highlights: "A potential advantage of this approach — compared to neutralizing antibodies — is its ability to capture and antagonize the effects of all the ligands that bind to FGFR1c, which include FGF1, FGF2 and FGF4."

FP-1039 is currently in a Phase II trial (ClinicalTrials.gov identifier: NCT01244438) for endometrial cancers with the S252W *FGFR2* mutation (the S252W mutation results in increased affinity and altered specificity of FGF binding). "There is a substantial body of literature suggesting that FGF2 is an angiogenic factor that may contribute to tumour angiogenesis, and may, in part, promote resistance to vascular endothelial growth factor (VEGF) and/or VEGF receptor targeting. This is the main rationale driving the clinical development of FP-1039," says Turner. "FGFs are also important in promoting cancer cell proliferation and survival through autocrine and paracrine loops. In addition, FGFRs can be activated by oncogenic activating mutations and amplifications. However, whether FP-1039 has the potential to target these mechanisms is less clear," he adds.

The paracrine FGF ligands bind to their receptors in conjunction with heparan sulphate proteoglycan (HSPG) cofactors, causing receptor dimerization and activation. Given the mechanism by which FGFs, FGFRs and cofactors form signalling complexes on the cell surface, Moosa Mohammadi, a structural biologist in the Department of Pharmacology, New York University School of Medicine, USA, has reservations regarding the understanding of the mechanism of action of the FGF ligand trap.

"The paracrine FGFs — which are the ones that the FGFR1c–Fc fusion protein is designed to trap — are prebound tightly to HSPGs and so they are sequestered on the cell rather than being present in circulation. Therefore, it is unclear how FP-1039 is trapping these FGFs," he says. Mohammadi adds: "In addition, FGFRs themselves have appreciable affinity for HSPGs, and therefore an FGFR1c–Fc fusion protein is most likely to also be immobilized in the extracellular matrix. Therefore, the inhibitory activity of the FGFR1c–Fc fusion protein could be simply due to the fact that it competes with the binding of paracrine FGFs for HSPG; that is, the FGFR1c–Fc fusion protein may be acting rather nonspecifically."

Although there might be uncertainties regarding exactly how FP-1039 works at a molecular level, the biologic has shown efficacy in preclinical *in vivo* studies. It inhibited FGF2- and VEGF-induced neovascularization, (AACR meeting 2007; abstract B55) and inhibited tumour growth in several cell line-derived xenograft models, including lung, colon and renal models (AACR meeting 2009; abstract 2789).