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Therapeutic requirements - chemokine receptor antagonists

Thomas J Schall of Chemocentryx gave an engaging keynote lecture in which he stated his belief that a golden age in the development of therapeutic modalities for inflammatory disease is just beginning, and that the chemokine system may be key to this. In the human genome 55 genes have been identified for distinct chemokines. The chemokine system is an attractive drug development target because of its natural selectivity and the knowledge that different chemokines in different tissues are associated with specific diseases. Furthermore, chemokine receptors belong to the seven-transmembrane-spanning GPCR class, which is historically known to be amenable to drug development. It has been hard to predict the therapeutic window for chemokine receptors, with only a small difference existing between non-effective and toxic levels. The A10 value, which is the amount of compound required in 100% serum to reduce migration ten-fold at any concentration of chemokine agonist, is a useful parameter, in addition to binding affinity, when considering chemokine antagonists.

Preclinical data were presented for CCR2 receptor antagonist CCX-140, which is anticipated to commence phase II trials for diabetes shortly. In Yorkshire swine treated with CCX-140 continuously at the A10 value for 28 days following bare metal stent implantation, restenosis was inhibited. This was an extremely healthy response, but the data showed that to be effective a high concentration of compound was required. In a rabbit intra-articular injection model of arthritis, a correlation was observed for CCX-354 (20 mg/kg) administration between consistent therapeutic effect and continuous A10 chemotaxis inhibition in 100% serum. This oral CCR1 antagonist is expected to enter phase II trials for arthritis shortly. The CCR9 antagonist CCX-807 (100 mg/kg bid) caused a maximal decrease in T-cell trafficking to the gut when the A10 value in 100% serum was covered.

Dr Schall described the 'A10 Con-Cov Rule', by which a full biological response can be elicited if a 'few' chemokine receptors remain unoccupied, stressing that most of the receptors must be covered by the drug for the majority of the time for this response to be blocked. This rule is not met by most anti-inflammatory chemokine compounds in clinical development, including CCR2 antagonist MK-0812 (c-6448; Merck), and CCR1 antagonists CP-481715, BX-471 (ZK-811752) and MLNM-3987, for reasons that include insufficient potency and oral absorption, CYP450 inhibition, hERG channel inhibition, excessively fast liver clearance and a lack of selectivity. In the past 15 years, only two antagonists targeting the chemokine system have been approved: maraviroc (Celsentri) and plerixafor (Mozobil), which respectively act at CCR5 and CXCR4.

CCX-282 (CCX282-B; Traficet-EN) is an orally active CCR9 chemokine receptor antagonist under development for the treatment of inflammatory bowel disease (IBD), in particular Crohn's disease (CD), and data from the induction phase of the PROTECT-1 trial of this compound, which involved approximately 120 test sites in 17 countries, were presented. In the induction stage of the trial (12 weeks), 436 subjects were randomized (1.5:1:1:1) to receive placebo twice daily or CCX-282B daily at 250 or 500 mg, or twice daily at 250 mg. At entry to the trial subjects required a CD activity index (CDAI) of greater than or equal to 250 and C-reactive protein (CRP) values of less than 7.5 mg/l. All patients were then treated with 250 mg of the compound twice a day for 4 weeks. Subsequently, CDAI responders (≥ 70-point drop) were randomized to placebo or 250 mg of the compound twice daily for 36 weeks; non-responders discontinued the trial at this time. Finally, a 4-week follow-up period occurred in which no drug was administered. Relative to placebo at 12 weeks, the 500 mg daily CCX-282B treatment demonstrated higher CDAI 70-point ($p = 0.039$) and 100-point ($p = 0.029$) response rates, irrespective of anatomic location, duration or concomitant treatment of CD; the two 250-mg dose regimens showed no difference from placebo. In addition the 500-mg dose demonstrated efficacy in previous non-responders to anti-TNF therapy. The CD endoscopic index of severity was also significantly lower for the CXC-282B-treated group at this dose at 12 weeks relative to placebo ($p < 0.05$), and there was no evidence of toxicity or immunosuppression: this dose was well tolerated. Dr Schall considered that this may be the first large-scale clinical example of therapeutic benefit in an inflammatory disease for a chemokine receptor antagonist.

Kinase inhibitor design

p38 is implicated in inflammatory responses and disease because of the role it plays in the modulation of TNF-alpha, IL-1beta, IL-6 and COX-2. Array BioPharma's Kevin Koch explained that it is becoming apparent that it also has a role in hematopoietic function and pain. First- and second-generation p38 inhibitors suffer from poor selectivity and

human whole blood (HWB) potency, with clinical adverse events including dizziness, rash, CNS toxicity and elevation of liver enzymes. Using the Delve program, consensus binding regions were identified using computational small fragment docking. An early lead from this effort was AR-190, which had p38 and HWB IC50 values of 60 and 1200 nM, respectively. In mice, this compound inhibited LPS-induced TNF-alpha production by 44% at a 30 mg/kg oral dose. Subsequently, ARRY-797 and ARRY-614 were generated with respective IC50 values of 7 and less than 2 nM for p38, and less than 2 and 14 nM for HWB. In a rat therapeutic model of collagen-induced arthritis (CIA), 10 mg/kg twice-daily treatment with ARRY-797 showed comparable efficacy to etanercept (Enbrel) at the same dose. In a murine bone fracture model, ARRY-797 at 30 mg/kg daily post-fracture reduced spontaneous guarding. This was comparable to the effect seen for celecoxib (Celebrex) at a 4 mg/kg daily dose post-fracture, but unlike celecoxib, there was no inhibition of callous formation. In a clinical post-surgical model of dental pain, ARRY-797 provided pain relief in a dose-dependent manner. ARRY-614 was shown to be effective at alleviating tactile allodynia in the rat breast carcinoma bone pain model MRMT-1, and it also decreased tumor bone destruction at a dose of 30 mg/kg; when this tumor line was grown subcutaneously in vivo, ARRY-614 did not inhibit its growth. ARRY-797 was shown to clinically lower CRP post-surgery, an effect that continued for several days; the decrease in CRP may be indicative of liver enzyme increases being off target. Dr Koch concluded that Array Biopharma has decided that p38 is not a viable target for the treatment of inflammatory disease.