EVALUATION OF AN ANTI-HUMAN IL-1 β ANTIBODY IN MONOSODIUM URATE CRYSTALS-INDUCED PERITONITIS MODEL IN hIL-1 β HUGEMM™ MICE

¹Xiaoyu An, ¹Kaixia Lian, ¹Jia Zheng, ²Fei Jian, ¹Henry Li, ¹Tao Yang*. ¹Crown Biosciences, Taicang, China; ²Shanghai Model Organisms, Shanghai, China

Background Gout is a chronic inflammatory disease featuring the deposition of monosodium urate (MSU) crystals in the synovial fluid of patients, followed by NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome activation and bioactive IL-1 β release, which recruits neutrophils to the local inflammation sites. Blocking IL-1 β function is becoming a potent therapeutic approach for gout and gouty arthritis. Conventional MSU-induced peritonitis in C57BL/6 mice provides a simple and rapid evaluation of therapeutics targeting inflammasome activation. However, this murine model has limitations when it comes to the evaluation of human-specific antibodies, for example, anti-human IL-1 β (anti-hIL-1 β) monoclonal antibodies (mAb). Thus, a murine model to assess the efficacy of anti-hIL-1 β mAb is needed. We have developed a hIL-1 β knock-in mouse model (hIL-1 β HuGEMM™), which is able to facilitate the pre-clinical evaluation of drugs targeting specific human biological molecules especially when mouse ortholog is not available. Therefore, an MSU crystals induced peritonitis model using hIL-1 β HuGEMM™ mice provides a robust model to evaluate therapies targeting hIL-1 β .

Methods MSU crystals were injected intraperitoneally into human IL-1 β (hIL-1 β) knock-in mice, where the coding sequence of mouse IL-1 β was replaced by hIL-1 β . Prior to MSU crystal administration, mice received treatment of either vehicle or anti-hIL-1 β antibody. Six hours facilitate post MSU crystal injection, serum and lavage flushed with PBS were collected. Subsequently, cytokine protein levels in the serum were determined by MSD, and the population of polymorphonuclear leukocytes (PMNs) (live CD11b+ Ly-6G^{Hi} cells) in the lavage was analysed by flow cytometry.

Results The vehicle treatment group showed a dramatic increase in hIL-1 β secretion and PMN leukocytes, in comparison to the group that did not receive MSU, which suggests a successful induction of acute inflammatory response in the peritoneal cavity. In contrast, mice that received a single administration of anti-hIL-1 β antibody 24 hours prior to MSU injection exhibited a significantly lower level of hIL-1 β when compared to the vehicle treatment group, which implies that the anti-hIL-1 β mAb efficaciously neutralized hIL-1 β secretion. In addition, TNF- α and IL-6, two further cytokines downstream of IL-1 β , were significantly reduced in the anti-hIL-1 β mAb treatment group. However, the PMN leukocyte infiltration in the anti-hIL-1 β mAb treatment group did not change in comparison to the vehicle group.

Conclusions In this study, an MSU crystals-induced peritonitis model was successfully established in hIL-1 β HuGEMM mice, which has the potential to evaluate immune therapeutics with anti-hIL-1 β blockades.

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