INTRODUCTION: The chemokine fractalkine/CX3CL1 and its highly selective receptor CX3CR1 mediate critical physiological events during inflammatory responses. The fractalkine/CX3CR1 axis has been shown to play a key role in the pathogenesis and the progression of a large number of diseases in which imbalance of the immune response is frequently seen. Since our last review published in early 2010, the fractalkine/CX3CR1 axis has gained vast attention as a potential therapeutic target in the scientific community, which can be clearly seen in the large number of studies that have been published on this issue since then. AREAS COVERED: A Medline/PubMed search was performed to detect all recently published studies on the role of the fractalkine/CX3CR1 axis as a therapeutic target in a wide range of clinical diseases. EXPERT OPINION: Recently published studies further underline the high potential of the fractalkine/CX3CR1 axis as a major target for future treatment of pain, inflammation and cancer. However, no clinical trials on novel therapeutics targeting fractalkine or CX3CR1 have been initiated so far, so that the fractalkine/CX3CR1 axis does still not find application in daily clinical practice.