Inhibition of Lysosomal Cysteine Proteases by Gold Compounds: A Possible Mechanism for the Antiarthritic Activity of Au(I)

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Although Au(I) complexes have been used to treat rheumatoid arthritis for over 75 years, their mechanism of action is still poorly understood. The Au(I) may act at the cellular level, the transcriptional level, or through inhibition of pro-inflammatory and tissue destroying enzymes. In a biological setting, Au(I) interacts with cysteine and other thiol groups, especially those with low pK_a values such as the activated thiols in enzyme active sites. In particular, the cathepsins, a family of cysteine-dependent enzymes responsible for joint destruction in rheumatoid arthritis, are attractive possible biological targets of Au(I). This poster will present the results of our efforts to develop a more comprehensive understanding of the mechanism of action of Au(I) antiarthritic agents. The ability of a series of Au(I) complexes to inhibit the activity of the cathepsins and an initial investigation of the structural basis for the Au(I)-cathepsin interactions will be presented.