1. INTRODUCTION

The previous chapters in this volume describe the rationale for the therapeutic use of matrix metalloproteinase inhibitors (MMPI) in oncology and the experience to date with these agents. However, both experts and those new to the field will realize that matrix metalloproteinase (MMPs) are involved in other disease processes. Therefore, it is probable that inhibitors of MMPs will prove useful for the treatment of diseases other than cancer. This chapter is designed to provide a brief overview of the evidence suggesting the involvement of MMPs in other diseases and an update on preclinical experiments or clinical trials that indicate MMPI impede or alter the progression of these diseases. This article is by no means an exhaustive review of the large body of MMP work outside of oncology, but it is hoped that it will provide a useful starting point for investigators interested in applications of MMPI in disease processes other than cancer. Other more comprehensive reviews have been published (1–5), as has a
2. ARTHRITIS

Cartilage breakdown is a major component of the pathological process that occurs in patients with arthritis. Because MMPs are directly involved in the degradation of this component of the extracellular matrix (ECM), the use of inhibitors of MMPs is a logical approach for the treatment of the disease. Current treatments for osteoarthritis and rheumatoid arthritis reduce the inflammatory response in the joint and relieve pain, but do not halt the progression of the disease. That is, the degradation of the joint continues unabated in arthritis patients despite the best treatments currently available.

Inhibitors of MMPs have proven to be effective in the treatment of animal models of arthritis (7,8). Several of the MMPs have been implicated in this process (9,10), with MMP-3 (Stromolysin-1) considered a key target (11). One compound in clinical trials (BAY 12-9566) is an MMPI designed to inhibit MMP-3 although sparing collagenase-1 (MMP-1). The rationale given for this MMP-3 directed, MMP-1 sparing design for BAY12-9566 was that MMP-1 is widely distributed throughout the body. On the other hand, MMP-3 seems to be up-regulated mostly within the affected joints in patients with arthritis. Furthermore, MMP-3 has the ability to degrade collagen and aggrecan and activate other MMPs (11). As the field matures, it will be interesting to learn whether this approach proves successful. An alternative approach now seems possible, given the recently reported cloning of the gene for aggrecanase (12,13). Aggrecanase is another degradative enzyme thought to be critical to the pathological breakdown of the joint structure in patients with arthritis.

Whereas arthritis may be an obvious disease target for MMPI, no drug is currently approved for use in patients with this disease. The first disease indication with an FDA-approved drug is periodontal disease.

3. PERIODONTAL DISEASE

Periodontitis is an inflammatory process that is initiated by the microflora of the subgingival environment. It leads to the destruction of the structures that support the teeth, including the gingiva, periodontal ligament, root cementum, and alveolar bone (14). It is generally accepted that the destruction present in the disease is a result of the host response. Recent research suggests that a significant contributor to this destructive process is MMP-8 (14,15). MMP-8 is produced mainly by neutrophils, which is consistent with the inflammatory nature of the disease and the hypothesis that the host response is responsible for the tissue damage present in patients with periodontitis. MMP-13, also desig-