MMP inhibitors: Glimmers of hope amidst clinical failures

Among biotechnology investors, drugs that inhibit matrix metalloproteinases (MMPs) may seem like a mirage: a tantalizing possibility that remains forever out of reach. MMPs—enzymes critical for a variety of physiological and pathological processes—are theoretically some of the most promising targets for new drugs to combat cancer and inflammatory diseases, but a rash of high-profile clinical failures has left many drug developers wary.

Meanwhile, basic-research scientists are concerned that results from failed trials are being over interpreted, overshadowing important positive findings.

MMPs are enzymes able to degrade most components of the extracellular matrix such as collagens, elastins, laminins, fibronectins and the protein core of proteoglycans. Research in the field has exploded. Over two dozen different MMPs have been identified in humans to date, and searches in the Medline database, for example, show that the number of publications related to MMPs has more than doubled in the past few years, from 362 in 1997 to 856 in 2001.

Clinical trials thus far have focused on using MMP inhibitors to block angiogenesis in tumors, but MMP activity is also a hallmark of tumor metastasis, meaning that one drug may target two phases of cancer progression. In addition, MMPs are critical in inflammatory and degenerative processes, including rheumatoid arthritis, osteoarthritis, periodontitis, arterial restenosis after angioplasty and aneurysm development.

Within the past year, research has also implicated MMPs in asthma attacks, chronic obstructive pulmonary disease, multiple sclerosis and premature skin aging. And in January, we reported the involvement of an MMP in the epidermal growth factor-receptor activation pathway leading to cardiac hypertrophy, with clear therapeutic implications (*Nature Med.* **8**, 35; 2002), as well as the role of another MMP in the overproduction of mucus in response to Gram-positive bacteria found in the lungs of cystic fibrosis patients (*Nature Med.* **8**, 41;

2002).

But the intensified research effort is proving difficult to translate into therapeutic practice. Although Marimastat, the flagship product of the troubled company British Biotech, has shown positive results against prostate cancer in a Phase III clinical trial (*Nature Biotech.* **19**, 499; 2001), it has been the subject of at least four other failed Phase III trials. Nor is British Biotech's experience unique. Both Bayer and Pfizer have recently terminated Phase III MMP inhibitor trials against cancer.

All MMPs share a common active-site motif: in which three histidine residues bind to a zinc ion. Many of the inhibitors currently undergoing clinical

testing are small peptide mimics that chelate the zinc ion and block the function of the enzymes. Although drug developers are searching for more specific compounds that will block particular MMPs, Robert Thompson, a surgeon and MMP investigator at the Washington University School of Medicine, argues, "most conditions that we consider potential targets for MMP inhibitors ... really do involve multiple enzymes, and one might be better off with a broader spectrum of inhibition."

Although the broad-spectrum MMP inhibitors Marimastat, and its analog Batimastat, have been disappointing, new work suggests that they still hold medical promise. When prostate cancer metastasizes to bone, the tumor cells increase the turnover of bone tissue, producing both osteolytic and osteoblastic effects. Using a chimeric mouse model of this process, researchers at Wayne State University found that batimastat reduces the osteolytic effect and inhibits growth of the tumor cells (*JNCI* **94**, 17; 2002). "[We] used a broad-spectrum inhibitor in an osteolytic model. The next obvious step would be a broad-spectrum inhibitor in an osteoblastic model," says lead investigator Michael Cher.

Normal X-ray

Osteolytic/osteoblastic changes caused by metastases

But the team may need to find a new drug for the next phase of the research. "Initially, British Biotech provided the drug free of charge," says Cher, but now "I can't even get it," as the company has limited the distribution of batimastat as part of its restructuring. Cher worries that the failed clinical trials are casting a pall over the field, even though "there are many ... mitigating factors in those few clinical trials that have been done," making the results difficult to interpret.

Maybe they should try tetracyclines. In an interesting twist, researchers have found that this old class of antibiotics acts as broad-spectrum MMP inhibitors. Indeed, the only MMP inhibitor so far approved as a drug, Collagenex's Periostat, is a tetracycline for the treatment of periodontitis. The company is now testing tetracycline derivatives against cancer.

Not only are clinical data for tetracyclines well established, but their broad spectrum of activity makes them a useful test-bed for MMP inhibition. For example, Thompson's group found that MMP-9 expression increases dramatically during the development of abdominal aortic aneurysm (AAA), probably linked to a degradation of aortic-wall elastin and collagen. In mouse and rat models, the team showed that doxycycline slows the progression of the condition, and initial studies have provided encouraging results that the antibiotic also reduces MMP levels in humans with AAA (*Ann. NY Acad. Sci.* **878**, 159; 1999).

Using an approved drug to test the mechanism allowed the research to move into the clinic quickly, but it could have unintended consequences: "One of our concerns is that people will just start to use [doxycycline as a treatment for aneurysms] based simply on what's in the literature," says Thompson. The team hopes to begin a multicenter placebo-controlled trial of doxycycline for AAA this year. If successful, the oasis on the MMP horizon may finally draw closer.

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