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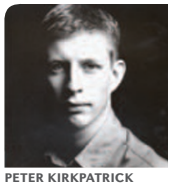
► **COVER:** 'Matrix metalloproteinase inhibitors' inspired by the Review on p480.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The expiry of patents for a number of first-generation biotech therapies has brought the scientific and regulatory challenges associated with potential approval of follow-on biologics to the fore. In this issue, Janet Woodcock and colleagues from the FDA's follow-on working group provide a historical perspective of the assessment of selected second-generation protein products with a view to illustrating the FDA's perspective on these challenges. An exciting new class of biotech therapies are those based on small interfering RNA (siRNA), which are currently being tested in clinical trials for several indications. De Fougerolle and colleagues present a progress report on the current challenges in the development of siRNA therapies, with a focus on siRNA identification, formulation and strategies to facilitate targeted delivery. An important consideration for the delivery of bioactive molecules (for example, proteins, antibodies and siRNA) is the influence of the microenvironment in which the target cells reside. In particular, the extracellular matrix (ECM) component of their cellular niche can be disrupted by disease. Kong and Mooney discuss the importance of cell–ECM interactions, and how recent insights may lead to new criteria for drug delivery systems. Matrix metalloproteinases (MMPs) are central to ECM biology, and have been recognised as important players in cancer and inflammation. Although initial trials for cancer therapy have been disappointing, MMP inhibitors might lead to new therapies for acute inflammatory and vascular diseases. Hu and colleagues compare the different classes of MMP inhibitors, and discuss their potential for diseases ranging from atherosclerosis to hepatitis. And in our final review, Mazanetz and Fischer highlight the potential of targeting tau hyperphosphorylation as a therapeutic strategy for neurodegenerative disorders such as Alzheimer's disease and review the development of specific inhibitors of the kinases that phosphorylate tau.

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