

A13 Proteases as drug targets

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Proteases make good drug targets, or do they? The effective management of AIDS with HIV protease inhibitors, or the use of ACE inhibitors to treat hypertension, are two examples of inhibitors that together generate annual sales of several billion dollars. On the other hand, matrix metalloproteinase inhibitors from several companies have in recent years failed in cancer and rheumatoid arthritis clinical trials. Looking forward, one might anticipate that the vast repertoire of proteases discovered through mining the human genome would yield many more that are causal in disease processes and therefore represent good drug targets - especially if the existing knowledge about developing inhibitors for most classes of protease can be applied. This overview will explore the opportunities and challenges that lie ahead, as well as some of the new methodologies that may be applied. It will discuss the tractability of proteases as targets from a chemistry perspective and it will also examine the feasibility of targeting proteases in terms of where they lie on pathophysiological pathways. It will also consider the impact that biologics are having on drug discovery and in particular whether biologically derived therapeutics such as antibodies are likely to significantly alter the way we view proteases as targets and the traditional ways in which therapeutic inhibitors have been developed.