Editorial

Proteases are important for maintenance of physiological functions in the body. A dysregulation of their activity can sometimes be detrimental to the normal physiological functions resulting in diseases specific to the activity of the proteolytic enzyme involved. Structure-based design has been the hallmark of protease inhibitor design work leading to identification of potent and selective inhibitors within as well as between various classes of proteases. Although most of the early work in the design of protease inhibitors involved peptidomimetic scaffolds, there is an increasing emphasis to develop nonpeptidic inhibitors that may provide better pharmacokinetic profiles. This issue, devoted to protease inhibitors, highlights the advancements in extremely important therapeutic areas.

The emergence of HIV protease inhibitors has dramatically altered the course of the mortality associated with HIV infection. The emergence of new resistant viral strains combined with noncompliance associated with side effects and heavy dosing schedules, present a formidable challenge in the treatment of this disease. The authors describe the development of the next generation of HIV protease inhibitors that surpasses the limitations of current antiviral treatments and has shown promise in the clinic.

Alzheimer's disease, a neurodegenerative disorder has attracted tremendous attention with the discovery of aspartyl proteases such as β-and γ-secretases that are involved in the cleavage of Aβ precursor protein to amyloid β peptides that form plaques, a pathological feature of Alzheimer's disease. Based on pioneering work described herein, by Ghosh *et al*. in identifying peptidic scaffolds for β-secretase, a number of companies have patented inhibitors that are modifications of these scaffolds. It is hoped that these drugs will address mortality issues that are not met with standard acetyl cholinesterase inhibitors that address only the cognitive functions.

Diabetes is a multifactorial disease associated with increase in cardiovascular disease, renal dysfunction, and nephropathy. The association of the most commonly used antidiabetics such as PPAR modulators with weight gain and edema has necessitated the development of approaches that would offer beneficial advantages. Potentiation of endogenous GLP-1 by inhibiting its degradation using DPPIV inhibitors has gained momentum as the next generation of antidiabetics. The authors have provided an overview of structural classes of DPPIV inhibitors along with discussion of binding modes. Promising clinical data from several companies has also been discussed.

The development of cathepsin K inhibitors for the treatment of osteoporosis has received considerable attention. The high expression of this enzyme in osteoclasts along with genetic studies highlights the importance of this enzyme in osteoporosis. The authors describe the evolution of simple aldehyde based inhibitors to potent, selective and orally bioavailable ketoamide-based inhibitors with *in vivo* efficacy. There are several companies with compounds in the clinic that demonstrate *in vivo* efficacy in postmenopausal women.

Deep vein thrombosis and pulmonary embolism are major causes of morbidity and mortality. Although heparin and warfarin are drugs commonly used for treatment, these have significant downsides. The review on coagulation cascade focuses on inhibitors of factor Xa, a key enzyme common to both the intrinsic as well as extrinsic pathways. In addition, the review also covers direct thrombin inhibitors. The review focuses mainly on clinical aspects of the drugs that have potential for treatment of these ailments.

Caspases are aspartyl proteases that are involved in apoptosis. Imbalance of the apoptotic pathway results in the pathogenesis of diseases including inflammation and cancer. The review on caspases focuses on recent advances in the field with emphasis on drugs in the clinic. Since these enzymes regulate cell survival and are also ubiquitous, outcomes of these clinical trials are eagerly awaited.

I would like to thank all the authors for their enthusiasm, time and dedication in helping to put this issue together. The topics covered in this issue will certainly benefit many of those who are engaged in areas specific to proteases and I hope would provide stimulating reading for the general reader

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