In summary, rodent PH animal models have been highly predictive for clinical trials with PH patients testing sGC stimulators. PVR and the corresponding increased pulmonary blood pressure were significantly decreased in both rodents and patients.

2.5 Thrombotic Diseases

Anticoagulant drugs are effective standards of care for the prevention and treatment of thromboembolic disorders. Among other drawbacks, the use of traditional agents like heparins is limited by their parenteral route of administration or by a significant variability of pharmacodynamic responses requiring routine monitoring and dose adjustments like with vitamin K antagonists (Laux et al. 2009). In addition, anticoagulants with broad effects on multiple coagulation factors display a narrow dose range between antithrombotic efficacy and the risk of increasing the rate of severe bleedings. Demonstrating and identifying this therapeutic window is the most important challenge to preclinical and early clinical models of thrombosis and hemostasis.

The search for selective novel oral anticoagulants (NOACs) has led to the discovery and successful development of direct inhibitors of coagulation factor Xa (FXa: rivaroxaban, apixaban; Perzborn et al. 2005; Wong et al. 2008) and of thrombin (FIIa: dabigatran; Wienen et al. 2007). FXa has a key function in blood coagulation because it initiates the final common pathway of coagulation by catalyzing thrombin generation. Thrombin is the central protease in the cascade leading to fibrin clot formation and platelet activation. Biochemical assays on isolated enzymes and on protease complexes as well as functional test systems in plasma and in whole blood provide data on the activity of each step in the coagulation system and the modulation by anticoagulants (Fig. 1).

In contrast to other organ systems, excellent access to the target tissue – the blood – both in experimental animals and humans allows early comparative assessment of compound activity profiles across species. This enables the selection of appropriate laboratory animals for studying effects of drug candidates in models of thrombosis and hemostasis. The FXa inhibitors rivaroxaban (Kubitza et al. 2013) and apixaban (Wong et al. 2011) show distinct in vitro potency profiles between species both biochemically on FXa (Ki) and functionally in plasma (prothrombin time, PT). Species dependency on clotting inhibition with dabigatran has been demonstrated in different coagulation tests (Eisert et al. 2010).

2.6 Animal Models for Anticoagulation Testing

After careful selection of the appropriate animal species and depending on the mode of action and on the intended clinical indication, the following criteria need to be considered from a range of thrombosis models: