In this issue of *Thrombosis and Haemostasis* a collection of review articles and original contributions have been published coinciding with the “17th International Congress on Fibrinolysis and Proteolysis” to be held in Melbourne, Australia, at the end of March 2004. It is widely acknowledged that the field of fibrinolysis and proteolysis has enormously expanded since the early discoveries of, for example, tissue type plasminogen activator (t-PA), urokinase receptor or plasminogen activator inhibitor-I (PAI-1): Research activities during the last decade have (a) uncovered detailed views about the 3D-structure of this and other inhibitors (1), (b) laid the basis for understanding the patho-physiological role of fibrinolytic components (particularly based on animal experiments with gene knock-outs and transgene models) (2, 3) and (c) strengthened the clinical use of different types of thrombolytic agents in the therapy of thromboembolic complications or of atherothrombosis (4). Together with the discovery of new cellular receptors and regulatory pathways in fibrinolysis (5, 6) as well as the interrelation of this system with other gene superfamilies of matrix metalloproteinases and their inhibitors (7, 8) or ADAMs (9), new exciting future developments are expected. These will influence our mechanistic thinking not only in haemostasis but also in other areas of vascular biology and medicine such as in angiogenesis or inflammation, in morphogenesis or tumor progression and metastasis where these proteolytic systems appear to play key roles in cellular communications. Nevertheless, the central aspects of fibrinolysis (and thrombolyis) and the different facets of humoral and cellular regulation remain a matter of intense research and of utmost clinical importance.

This theme issue contains three review articles which concentrate on different aspects of the important fast acting inhibitor of the plasminogen activation system, i.e. PAI-1, whose multiple functions in the extracellular environment (both related and unrelated to proteolysis) strongly depend on surface-related interactions with plasma membrane or with extracellular matrix components such as vitronectin (10, 11). Ann Gills and Paul Declerck (12) summarize recent developments in structure and function of PAI-1, particularly concentrating on mutagenesis studies and the upcoming therapeutic potential of “PAI-1-inhibitors”, based on the fact that elevated levels of PAI-1 appear to be a risk factor in situations of atherothrombosis (13). Yet, in PAI-1-deficient, atherosclerosis-prone animals, increased growth and matrix remodeling of advanced lesions was found (14), indicative of the fact that PAI-1’s multiple functions differentially contribute to various patho-physiological situations.

In addition to its prominent role as primary inhibitor of t-PA and urokinase, PAI-1 plays an important role in cancer since (besides its antiproteolytic function) it was found to regulate cellular adhesion and migration and thereby contributes to mechanisms of tumor progression and metastasis including (tumor) angiogenesis (15). From a mechanistic point of view many facets of PAI-1 are still incompletely characterized in this context: The inhibitor is not only recruited from different cellular sources (including expression in adipocytes, liver, vascular cells or secreted by platelets), but its stability and functional lifetime is determined by the association with extracellular components or its connection to cellular adhesion receptors (such as the urokinase receptor or integrins) (16). Peter Andreasen and colleagues (17) summarize novel aspects devoted to cellular activities of PAI-1 in relation to tumor cells. To round up this subject from a medical point of view, Nadia Harbeck and co-workers (18) present important clinical data as to the diagnostic and prognostic impact of determinations of fibrinolytic factors in the context of human tumor entities such as breast cancer. Here, the initial work by the Munich Group as well as by other colleagues in Ireland and Denmark paved the way for the...
prognostic potential of fibrinolysis-related components in cancer. Based on these concepts, a number of (low molecular weight) inhibitors are currently being tested for their potential role as anti-tumor agents (19).

Since most of the secrets of life are still hidden in our brain, and common molecular aspects are apparent between blood vessels and nerves (20), it is not surprising that a “neuroserpin” is expressed in the central nervous system that primarily inhibits t-PA (21). Together with the “non-fibrinolytic” functions of t-PA as modulator of neuromolecular signals (22), new aspects of neuroserpin biology and possible applications in the treatment of cerebral ischemia are presented by Manuel Yepes and Daniel A. Lawrence (23). These aspects are a very good example of how novel discoveries open our eyes towards areas “beyond haemostasis” where known components meet new molecular partners and change our way of thinking. Here, the biological concept of dealing with different “fibrinolytic compartments” is applicable as well (24), and intracellular cytoskeleton-associated molecules such as myosin or vimentin (exposed following cellular activation or injury) appear to influence fibrinolytic reactions in a yet uncompletely understood manner (25, 26).

In conjunction with these four review articles, a number of original contributions will follow which, taking into consideration the limitations of this issue, clearly demonstrate the widespread importance the fibrinolytic factors may have, such as, in prion protein-related proteolysis, in processes related to ischemia reperfusion injury, or in novel aspects of thrombin activatable fibrinolysis inhibitor (TAFI) as regulator of fibrinolysis and potential marker in vascular disfunctions.

References