Since the isolation of protein S in 1979, initial studies demonstrated that protein S acted as a natural anticoagulant by promoting the serine protease activity of activated protein C (APC) on its substrates, the coagulation factors Va and VIIIa. This interaction required binding to phospholipid membranes through the vitamin K-dependent Gla residues of protein S. Later work showed that protein S interacts with other blood components, including a regulator of complement (C4b-binding protein), other components of the coagulation cascade (tissue factor pathway inhibitor and factor Xa), plasma lipoproteins and cells. The later interaction is mediated through specific membrane receptor tyrosine kinases belonging to the TAM family. This choreography of interactions predicted new biological functions, and protein S is now recognised as a regulator of essential processes in the response to damage, including regulation of phagocytosis of apoptotic cells (efferocytosis), cell survival and activation of innate immunity.

Still, the anticoagulant function of protein S is central to its biological role, as it was first proposed by the association of protein S deficiency and thrombosis in human cohorts. This has been experimentally corroborated by the recent characterization of the protein S knockout mouse phenotype. In the present issue of *Thrombosis and Haemostasis*, Heeb et al. provide further evidence of the use of protein S in therapeutic anticoagulation independently of the infusion of APC.

One of the reasons behind the late recognition of the APC-independent anticoagulant function of protein S derives from basic biochemical reasons. This functional property depends on the presence of Zn2+ ions, which were often removed during protein S purification procedures. The present study shows promises of using protein S as an anticoagulant drug on its own, independently of APC. This would add a new therapeutic substance that could be especially interesting for situations where control of both anticoagulation and inflammation has to be provided. This includes treatments for sepsis and atherosclerotic disease, were the role of protein S has been recently evaluated. Protein S is a complex molecule with several posttranslational modifications, and needs suitable animal models where its functional requirements are validated. The present work is an important step forward in this direction.