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**Binding Mode of Tick Anticoagulant Peptide Complexed to Factor Xa
and the Implication of the Structure to Drug Discovery**

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Thrombotic diseases, including stroke, deep vein thrombosis, and pulmonary embolism, are a major cause of death and morbidity. Coumadin is the only marketed oral anticoagulant agent, even though the drug suffers a narrow therapeutic window. fXa, a trypsin-like serine protease plays a vital role in the regulation of normal homeostasis and abnormal intravascular thrombus development. The location of fXa at the intersection of the intrinsic and extrinsic paths of coagulation cascade makes it an attractive antithrombotic drug target. Recombinant tick anticoagulant peptide (rTAP) is a competitive, slow, tight-binding inhibitor of factor Xa. The sequence of rTAP, including six cysteine residues, suggests that it is related to the Kunitz class of serine protease inhibitors. Nevertheless, TAP is clearly a novel inhibitor of factor Xa because it does not inhibit trypsin, thrombin or any other serine proteases. The structure of the complex between rTAP and fXa and the implication of the structure to drug discovery will be discussed.