

innovations

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TITLE: CRYSTAL STRUCTURE OF FACTOR VAI AND METHOD OF IDENTIFYING BLOOD FACTOR VA MODULATORS

INVENTOR: Stephen Everse, et al.

DESCRIPTION: The structure (the coordinates) of bovine factor Vai reveals for the first time the domain organization and more importantly the atomic positions of atoms forming the structure. Factor Vai is a physiological relevant inactivation product of factor Va produced by activated protein C. Purified bovine factor Vai in 20 mM HEPES, 150 mM NaCl, 2 mM CaCl₂ (pH 7.4) was crystallized at ~6.5 mg/mL by the vapor diffusion sitting-drop method at 12°C against 200 mM MgCl₂, 16% PEG 3350 (pH 5.0). After 5-21 days, diffraction quality crystals appeared. Three isomorphous heavy atom derivative crystals were identified from native crystals soaked in mother liquor containing either 10 mM tetrakismercuroxymethane (TAMM), 10 mM ethylmercury (EtHg) or 2.5 mM lead acetate (PbAc).

ADVANTAGES: Prior to this structure models of factor Va were built on homologous proteins. Though they were fairly accurate in determining the fold of the individual domains they did not correctly identify the domain organization and therefore the more subtle interactions that take place. Nor were the models able to correctly identify the location of a bound copper atom.

POSSIBLE COMMERCIAL APPLICATIONS: Factor Va serves as the cofactor in the prothrombinase complex that results in a 300,000 fold increase in the rate of thrombin generation compared to factor Xa alone. In its role, factor Va interacts with both factor Xa and prothrombin. Structural based design of therapeutics continues to be a productive commercial avenue for the design of new drugs. The best known example of this are the inhibitors designed for the HIV protease which are still some of the most effective drugs to date. In addition, with the high degree of identity shared between factor Va and factor VIIIa (hemophilic factor) it would be appropriate to also use this structure to build models of factor VIIIa and use that to design potential therapeutics.

PATENT STATUS: Patent pending

LICENSING STATUS: World wide rights available

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