

W0200

**The Crystal Structure of Factor Va: A New Mechanism for Membrane Binding and Function.** T.E. Adams<sup>1</sup>, M.F. Hockin<sup>2</sup>, K.G. Mann<sup>1</sup>, S.J. Everse<sup>1</sup>, <sup>1</sup>College of Medicine, Univ. of Vermont, Burlington, VT 05401 USA, <sup>2</sup>Howard Hughes Medical Institute, Univ. of Utah, Salt Lake City, UT 84112 USA.

The cofactor protein factor V is directly involved in regulating the production of  $\alpha$ -thrombin to maintain vascular integrity and hemostasis. When activated, factor Va interacts with the enzyme, factor Xa, to form the *prothrombinase* complex on a membrane surface and convert prothrombin to  $\alpha$ -thrombin. Once sufficient  $\alpha$ -thrombin has been generated factor Va is inactivated by the anticoagulant protein APC, resulting in factor Va<sub>i</sub>. We have solved the crystal structure of factor Va<sub>i</sub> at 2.8 Å resolution using a combination of MIRAS and molecular replacement. Crystals are orthorhombic, space group P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub> with cell dimensions:  $a = 63.37$ ,  $b = 86.56$ ,  $c = 229.20$  Å. Composed of two ceruloplasmin-like A domains and two discoidin-like C domains, the overall structure resembles a distorted butterfly where both of the C domains form the lower wings and can interact with a membrane surface. This is contradictory to previous electron microscopy and homology models suggesting the C domains stacked upon each other and provides a new foundation for understanding of factor V's role in regulating how blood clots.

This work is supported by the NIH, American Society of Hematology and DOE-EPSCoR.