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**Conformational Complexity of Complement Component C3.** Bert J.C. Janssen<sup>1</sup>, Eric G. Huizinga<sup>1</sup>, Hans C.A. Raaijmakers<sup>1</sup>, Anja Roos<sup>2</sup>, Mohamed R. Daha<sup>2</sup>, Kristina Nilsson-Ekdahl<sup>3,4</sup>, Bo Nilsson<sup>3</sup>, Piet Gros<sup>1</sup>, <sup>1</sup>Crystal and Structural Chemistry, Bijvoet Center for Biomolecular Research, Utrecht Univ., The Netherlands, <sup>2</sup>Dept. of Nephrology, Leiden Univ. Medical Center, The Netherlands, <sup>3</sup>Dept. of Clinical Immunology, Univ. Hospital, Uppsala, Sweden, <sup>4</sup>Dept. of Chemistry and Biomedical Sciences, Univ. of Kalmar, Sweden.

The mammalian complement system plays a key role in innate and adaptive immunity. The activation of its central component C3 (1,641 residues), results in inflammation and elimination of self and non-self targets. Recently we solved the structures of native C3 and its major proteolytic fragment C3c. First, C3c, purified from outdated human plasma, was solved by SIRAS and MAD phasing. Multi-crystal averaging using nine partial masks was required to obtain an interpretable electron-density map. Second, C3, purified from fresh human plasma, was solved by molecular replacement. Initial positioning of C3c or any of its fragments was unsuccessful. However, the  $\alpha 6$ - $\alpha 6$  barrel structure of C3d (18% of C3) was positioned correctly and gradually the domains of C3c could be placed. The structures show that C3 consist of thirteen domains, of which nine were unpredicted and that the central core consists of eight structural homologous domains. Large and surprising structural rearrangements are observed in going from C3 to C3c, indicating an unprecedented, conformation-dependent mechanism of activation and deactivation of C3.