

## 21. Derivatives of Human Complement Component C3 for Therapeutic Complement Depletion: A Novel Class of Therapeutic Agents

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**Abstract.** To obtain proteins with the complement-depleting activity of Cobra Venom Factor (CVF), but with less immunogenicity, we have prepared human C3/CVF hybrid proteins, in which the C-terminus of the  $\alpha$ -chain of human C3 is exchanged with homologous regions of the C-terminus of the  $\beta$ -chain of CVF. We show that these hybrid proteins are able to deplete complement, both in vitro and in vivo. One hybrid protein, HC3-1496, is shown to be effective in reducing complement-mediated damage in two disease models in mice, collagen-induced arthritis and myocardial ischemia/reperfusion injury. Human C3/CVF hybrid proteins represent a novel class of biologicals as potential therapeutic agents in many diseases where complement is involved in the pathogenesis.

### 1 Background and Concept

Cobra Venom Factor (CVF) has long been known to be a structural analog of a complement component C3 (Vogel 1991; Vogel et al. 1984, 1996). Both C3 and CVF are synthesized as single-chain pre-pro-proteins that are subsequently processed into the mature two-chain C3 protein, and the mature three-chain CVF protein, respectively (de Bruijn and Fey 1985; Fritzingler et al. 1994). The two proteins share extensive sequence similarity, at both the protein and DNA levels. CVF and human C3 are approximately 50% identical at the protein level and approximately 70% similar if one allows for conservative replacements (Fritzingler et al. 1994). The structural homology between cobra C3 and CVF is even greater;