SIGNIFICANCE STATEMENT

Atypical hemolytic uremic syndrome (aHUS) and C3 glomerulopathy (C3G) are caused by overactivation of the alternative pathway of complement and have poor prognosis, often leading to ESRD. Therapeutic options for these diseases are limited. This manuscript describes a novel synthetic fusion protein, MFHR1, combining proximal and terminal cascade inhibition activities and the ability to form multimeric complexes. MFHR1 shows strong inhibitory capacity *in vitro* and ameliorates experimental C3G in a factor H knockout mouse model *in vivo*. MFHR1 might, therefore, offer a novel basis for therapeutics in complement-associated diseases.