Project Title: Structure-function analysis of a cytomegalovirus CC chemokine

Project Abstract:
For most end-organ diseases, transplantation represents the last resort for treatment. A major problem for long term survival of transplant recipients is chronic rejection, a process that is driven largely by immunomodulatory proteins called chemokines. Infection with human cytomegalovirus (HCMV) accelerates chronic rejection, and this may be due in part to the ability of the virus to alter the expression of host chemokines. However, it has recently been appreciated that the HCMV gene UL128 encodes a protein that shares amino acid sequence features with a class of human chemokines. One hypothesis is that this virally encoded chemokine activity contributes to accelerated graft rejection. In support of this hypothesis, the rat CMV homologue, r129 has been shown to have chemokine activity. Both UL128 and r129 are larger than typical host chemokines, with extended C-terminal sequences that may relate to other functions of these proteins. It is clear that the UL128 protein also plays a role in determining tropism of the virus by facilitating entry into specific cell types. This leads to the hypothesis that the chemokine and entry functions of UL128 reside on separate domains. The goal of the proposed studies is to generate methods and reagents to conduct structural analyses of r129 and UL128. Detailed structural understanding of these proteins will allow for formulation of testable hypotheses regarding the functions of these proteins, as well as the design of mutants for use in studies of HCMV-related pathologies.