Instabilities and irregularities promote virulence in Group A *Streptococcus* M1 protein

McNamara, C.[1], Zinkernagel, A.S.[3], Macheboeuf, P.[1], Cunningham, M.[5], Nizet, V.[3,4], Ghosh, P.[1,2]

[1]Department of Chemistry & Biochemistry, [2]Section of Molecular Biology, and [3]Department of Pediatrics and [4]School of Pharmacy & Pharmaceutical Sciences, University of California, San Diego, La Jolla, California 92093, USA [5]University of Oklahoma Health Sciences Center, Biomedical Research Center, 975 NE 10th StreetOklahoma City, Oklahoma 73104, USA

Antigenically variable M proteins are major virulence factors and immunogens of the leading human pathogen Group A *Streptococcus* (GAS). Here we report the ~3 Å resolution crystal structure of a GAS M1 fragment containing regions responsible for eliciting type-specific, protective immunity and for binding fibrinogen, which promotes M1 proinflammatory and antiphagocytic functions. Nonidealities in the coiled-coil sequence of M1 create significant structural irregularities and behavioral instabilities, closely mimicking idiosyncrasies in myosin and tropomyosin and explaining patterns of crossreactivity in autoimmune sequelae of GAS infection. Sequence idealization of a large segment of the M1 coiled coil enhances stability, but diminishes fibrinogen binding, proinflammatory effects, and antibody crossreactivity while leaving protective immunogenicity undiminished. These results suggest the use of idealized M proteins as vaccine immunogens.