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Hierarchical Cluster Formation in Concentrated Monoclonal Antibody Formulations P. DOUGLAS GODFRIN, University of Delaware, JONATHAN ZARZAR, ISIDRO (DAN) ZARRAGA, Genentech, Inc., LIONEL PORCAR, PETER FALUS, Institute Laue-Langevin, NORMAN WAGNER, University of Delaware, YUN LIU, NIST Center for Neutron Research, University of Delaware — Reversible cluster formation has been identified as an underlying cause of large solution viscosities observed in some concentrated monoclonal antibody (mAb) formulations. As high solution viscosity prevents the use of subcutaneous injection as a delivery method for some mAbs, a fundamental understanding of the interactions responsible for high viscosities in concentrated mAb solutions is of significant relevance to mAb applications in human health care as well as of intellectual interest. Here, we present a detailed investigation of a well-studied IgG1 based mAb to relate the short time dynamics and microstructure to significant viscosity changes over a range of pharmaceutically relevant physiochemical conditions. Using a combination of experimental techniques, it is found that upon adding Na_2SO_4, these antibodies dimerize in solution. Proteins form strongly bounded reversible dimers at dilute concentrations that, when concentrated, interact with each other to form loosely bounded, large, transient clusters. The combined effect of forming strongly bounded dimers and a large transient network is a significant increase in the solution viscosity. Strongly bounded, reversible dimers may exist in many IgG1 based mAb systems such that these results contribute to a more comprehensive understanding of the physical mechanisms producing high viscosities in concentrated protein solutions.

P. Douglas Godfrin
Massachusetts Institute of Technology

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