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Mechanistic insights into protein aggregation and the development of rational approaches and predictive tools to stabilization of biopharmaceuticals

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Stabilization of biopharmaceutics is frequently performed empirically based on correlating process parameters with changes in biological activity. However, most probably this approach will be insufficient for biosimilars. The rational stabilization of biotherapeutics requires understanding the mechanism of degradation as well as the efficacy, stability, feasibility and performance of the biopharmaceutics. For instance, aggregation could cause immunogenicity and reduce the efficacy of the drug, and therefore, elucidating the protein stability and aggregation is very important for developing successful formulations. We investigated the stability and aggregation of several therapeutic monoclonal antibodies (mAbs) with accelerated studies utilizing SEC-HPLC, fluorescence, light-scattering spectroscopy, and TEM to detect the concentration and conformational change of the monomer, aggregate formation, and sizes of the species formed upon temperature stress. Results indicate that the protein aggregation is accompanied by partially unfolded proteins and that the aggregates consist of many sizes. The conformation of the proteins within aggregates changes with aggregate size. Based on experimental results, we developed a protein aggregation mechanism, which could be used to analyze mAb aggregation kinetics. In addition, the lack of a fast selection method to identify the most stable protein is one of the major challenges for developing successful therapeutic protein formulations more rapidly. Accurate detection of small amounts of aggregates is another problem. I will present an alternative method for initial screening of the aggregation propensity of proteins, using mAb as an example and ANS / ThT binding.

Biography

Kayser completed his PhD at the University of Leeds in the UK, in the School of Chemistry in 2004. He then did two postdoctoral studies: first at the Max Planck Institute of Biochemistry in Germany and then at MIT studying protein folding and aggregation, particularly with monoclonal antibodies, and formulation development. Subsequently, he stayed at MIT as a senior scientist working on vaccine formulation and method development as well as particle size analysis. He has published more than 15 papers on the subject in reputed journals and serves as an associate editor of Open Journal of Biophysics.

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