THE DEVELOPMENT OF THERAPEUTIC PROTEINS CAN BE HINDERED BY POOR DECISION-MAKING STRATEGIES IN THE EARLY STAGE

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In this study we address two major issues related to the current development process of therapeutic proteins and their characterization. First, due to limited samples amounts, the selection of lead molecules in the early stages is often based on the results from a limited physicochemical characterization. The latter can be based on measurements of only 2-3 parameters, e.g. protein melting temperature, protein aggregation temperature, and is usually performed in only one buffer, e.g. PBS. The hypothesis we present is that such approach can lead to the rejection of lead candidates that can still be manufacturable and can move on to clinical trials. The second matter we address are the often-reported correlations between protein physicochemical parameters in the literature. We propose that such correlations can be found only in a small sample population, e.g. one protein in different solution conditions or different proteins from the same class. However, we expect that such correlations would not be valid in a large population, including various protein structures and solution conditions.
In order to address the above-mentioned issues, we created the PIPPI consortium (http://www.pippi.kemi.dtu.dk) and applied systematic approach to map the physicochemical properties of a wide range of proteins and extensively study their stability as a function of the solution conditions.
We show that promising therapeutic protein lead candidate can appear as non-manufacturable when only limited physicochemical characterization is performed, e.g. a few methods are used and only a few solution conditions are tested. Therefore, the rejection rate during early-stage development can be improved by more thorough physicochemical characterization. Moreover, only weak linear correlations between biophysical properties of proteins are observed in a large populations. This suggests that the often-reported correlations between parameters describing the protein stability are not representative of a global population. Understanding the connections between various physiochemical parameters would require a systematic database which is currently in development by the PIPPI consortium.