Targeting IDPs: A Drug Discovery strategy for Intrinsically Disordered Proteins

Priyanka Joshi, Johnny Habchi and Michele Vendruscolo

Department of Chemistry, Lensfield Road, University of Cambridge, Cambridge CB2 1EW, United Kingdom (email: pj291@cam.ac.uk)

Although all the current major classes of proteins considered to be druggable are fully folded in their native states, intrinsically disordered proteins (IDPs) are becoming attractive candidates for therapeutic intervention by small drug-like molecules. IDPs are challenging targets since they exist as ensembles of structures, thereby making them unsuitable for standard rational drug design approaches, which require the knowledge of the three dimensional structure of the proteins to be drugged. We have investigated a strategy for the therapeutic treatment of neurodegenerative diseases by developing a computational fragment based drug design strategy to enable screening of drug-like compounds for intrinsically disordered proteins. The application is focused on Aβ, tau and alpha-synuclein, which are three IDPs associated with Alzheimer's and Parkinson's diseases. Small drug-like molecules in our fragment-based library provide insights into key molecular features in compounds binding Aβ, tau and alpha-synuclein, thereby opening gates to further investigation and identification of novel drugs for IDPs implicated in neurodegenerative disorders. To illustrate the potential of our approach we show, using biophysical methods and chemical kinetics, that molecules from this library are observed to have an effect on the aggregation behavior of Aβ. Finally, through this study, we aim to shed further light on the potential druggability of IDPs in general.