I will describe our research program involving the prediction of protein-protein interactions (PPIs). Underlying our general approach is the use of 3D-structural similarity to detect functional relationships between proteins. When combined with simple and fast filtering functions we are able to score billions of potential PPIs with relatively moderate computational demands. I will review how this is accomplished with focus on the development and application of our Predicting Protein-Protein Interactions (PrePPI) and Pathogen Host Interactions (P-HIPSTer) databases. Further, PrePPI has been integrated with PPIs inferred from reverse engineering algorithms from patient-sample genomic data to yield structure-informed cell and tumor-specific regulatory networks. Finally, we have used related methodologies to create the Predicting Protein Compound Interactions (PrePCI) database whose features will be described.