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A dream about wobbling proteins

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One of the most characteristic features of a drug lies in its specific interaction with a target biological molecule. The identifying of target molecules and discovery of small molecular compounds with affinity for them are the earliest and most difficult steps on the path toward the drug discovery. In these steps, random approaches where serendipity is the driver for success have been most frequently followed, and hence a lot of time and money have been spent. In this context, developments in structural biology gave us a great hope for totally changing the paradigm of drug discovery. But this hope has remained as a dream yet. Although 3D images of protein structures stimulate the imagination of chemists in designing drugs, their practical contribution to increased efficiency in drug discovery is still far from satisfactory. (Structure elucidation is clearly different from computer-aided drug design (CADD); however, the point is made, because our most important (perhaps, the only) objective in determining protein structure is to help us identify small molecular compounds with affinity for a target protein.)

As has been demonstrated in many examples, the main problem in CADD resides in the high flexibility of protein structures. It is often impossible to predict the structure of a complex of protein and small molecule based on the one of the protein obtained crystallographically. Protein structures are induced to change according to the bound small molecules. Such interaction is only interpreted *a posteriori*. Is 3D determination then useless for drug discovery? NO! In my view, the understanding of both flexible and rigid parts of a structure is crucial for drug discovery. A dynamic structure is the essence of protein function; enzyme catalysis, signal transduction by protein association, on-off switching by nucleotides, and so on all involve structural dynamics of proteins. Keys for drug discovery must be hidden there.

Protein structure should be studied for its wobble. By its nature, crystallography has pursued the path of restricting the flexibility of protein structure. Now it may be the time to focus on the wobble or mobility of proteins to gain a better understanding of their function, which will be of significant help for drug discovery. We hope that structural biology will tackle this important issue by employing various available methodologies.

I am watching several different compounds designed by CADD hitting at a wobbling target protein on a computer screen. After a few seconds, the wobbling of the protein stops suddenly when the protein seizes one of the small molecules. The affinity of the small molecule is determined to be good enough for a drug candidate. My elusive dream.