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Structural Biology and Fragment-based Drug Discovery. Tom L. Blundell, Dept. of Biochemistry, Univ. of Cambridge, Cambridge CB2 1QW and Astex Technology, Cambridge CB4 0QA, UK.

Knowledge of the three-dimensional structures of protein targets now emerging from genomic data has the potential to accelerate greatly drug discovery, but technical challenges and time constraints have traditionally limited their use primarily to lead optimization. Their application is now being extended beyond structure determination, into new approaches for lead discovery (for review see Blundell et al., 2002). Virtual screening coupled with high throughput X-ray crystallography is focused on identifying one or more weakly binding small-molecule fragments from compound libraries consisting of hundreds of small-molecule fragments. The high-resolution definition of this binding interaction provides an information-rich starting point for medicinal chemistry. The use of high throughput X-ray crystallography does not end there, as it becomes a rapid technique to guide the elaboration of the fragments into larger molecular weight lead compounds.

One major challenge for drug discovery arises from the very large surfaces that are characteristic of many of the protein complexes, for example those involved in receptor recognition and signal transduction (see for example, Pellegrini et al., 2000). This is especially true of complexes that are assembled from preformed globular domains. Not only is it difficult to bind a small molecule to the large, relatively flat surfaces of such proteins involved in protein interactions, but it is also difficult to disrupt the interaction entirely even if one did. It remains to be seen whether the emerging lead discovery approaches discussed in this lecture will prove suitable for these systems. However, recent analyses of multiprotein systems involved in cell regulation and signalling have identified a large number in which one component involves a flexible or unstructured region of the polypeptide chain. An example involves the complex of the human recombinase, Rad51, and the product of the breast cancer associated gene, BRCA2 (Pellegrini et al., 2003), which is not only scientifically revealing but offers an encouraging and perhaps more druggable site of interaction that could be used to target agents that would be helpful during chemo- or radio-therapy. We suggest that proteins forming interactions with a ligand that comprises a continuous region of flexible peptide may be more druggable targets than where complexes are formed from preformed globular protein structures.