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SAXS as an assay for protein:ligand interaction.

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Small-angle x-ray scattering (SAXS) is sensitive to the size and shape of macromolecules in solution. Whilst there can be some uncertainties involved in modelling macromolecular structure directly from SAXS data, relative changes in structure can be measured with a high degree of confidence.

The binding of a small-molecule ligand to a large protein in itself is generally too subtle an event to see with confidence by SAXS. In order to use SAXS as an assay for the interaction between a ligand and a protein one of the following cases must be true: 1) the ligand interaction causes a conformational change in the protein, 2) the ligand interaction disrupts a protein:protein interaction causing a change in multimerisation state or 3) the ligand itself is rather large by comparison to the protein.

On this basis I present three recent examples that explore the utility of SAXS to assaying the interaction between medically relevant proteins and various chemical ligands. These examples are: 1) the binding of lysine analogues with the human anti-clotting protein plasminogen that lead to a dramatic conformational change in the protein, 2) the interaction between a large branched polymer (dendrimer) and HIV gp120 that leads to a reduction in infection rates and 3) interaction between a novel allosteric inhibitor and HIV reverse-transcriptase that causes a subtle rearrangement in the domain structure of this protein and lead to inhibition of function.

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Summary

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