DNA-based molecular rulers: Probing the distance limit of bivalency

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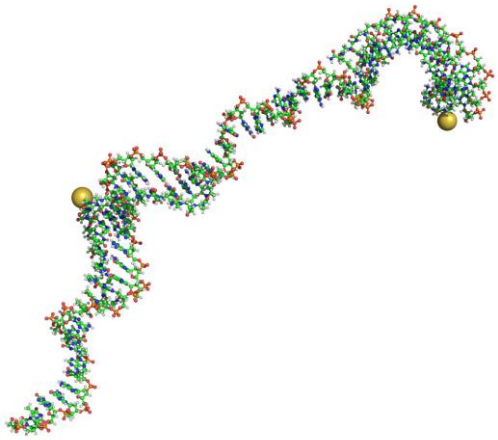

Abstract:

Multivalency is used by nature to strengthen weak receptor-ligand interactions. Tailor-made multivalent ligand systems that provide control over both the valency and the spatial arrangement of the ligand display have been used to study structural properties of the receptor. However, the range of interligand distances than can be accessed by using well defined scaffolds is limited. Polymers, liposomes and nanoparticles enable ligand presentation over nano-sized dimensions, yet the number and the spatial arrangement of the ligands actually involved in receptor binding cannot be predicted and it is, therefore, difficult to assess distance-affinity relationships. Owing to the above-mentioned limitations the distance limit of multivalent binding remained unexplored and it was unclear whether distance-matched bivalent or multivalent ligand systems still provide significant affinity enhancements when two or more targeted receptor binding sites are separated by very long and flexible linkers. In this research project, we will explore – for the first time – the distance limit of bivalency. Host-guest systems known from supramolecular chemistry will be mounted onto DNA-based scaffolds. The double helical DNA scaffold offers a unique set of properties, which are particularly useful for this study: a) bivalent ligand displays can be formed upon nucleic acid hybridization in a self-assembly process, which facilitates spatial screening, b) the spatial arrangement of the ligand display can be precisely controlled, c) the flexibility of the ligand display can be adjusted by integrating nick sites and unpaired template regions, d) DNA scaffolds provide for high solubility in biological media and e) the high persistence length of DNA duplexes confers structural integrity over nanometer sized distances. The project involves a collaboration with the Weber (C2) and Netz (C9) groups, who will assess the reach of bivalency by computational means.

Publication/s:

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C. Fasting, C.A. Schalley, M. Weber, O. Seitz, S. Hecht, B. Koksch, J. Dernedde, C. Graf, E.-W. Knapp, R. Haag: Angew. Chem. Int. Ed., 51(42):10472–10498, 2012