Multivalent inhibitors of carbohydrate-binding proteins

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Introduction

Protein-carbohydrate interactions at cell surfaces mediate many important processes in biology from fertilisation to adhesion of viruses, bacteria and their toxins. Individually, protein-sugar interactions are usually very weak, but both affinity and binding selectivity can be enhanced through a phenomenon called multivalency: multiple binding sites on the protein interact simultaneously with multiple copies of the sugar ligand to achieve a high avidity and enhance binding selectivity. The multivalency phenomenon can be reproduced using synthetic molecules that incorporate multiple copies of the carbohydrate ligands.

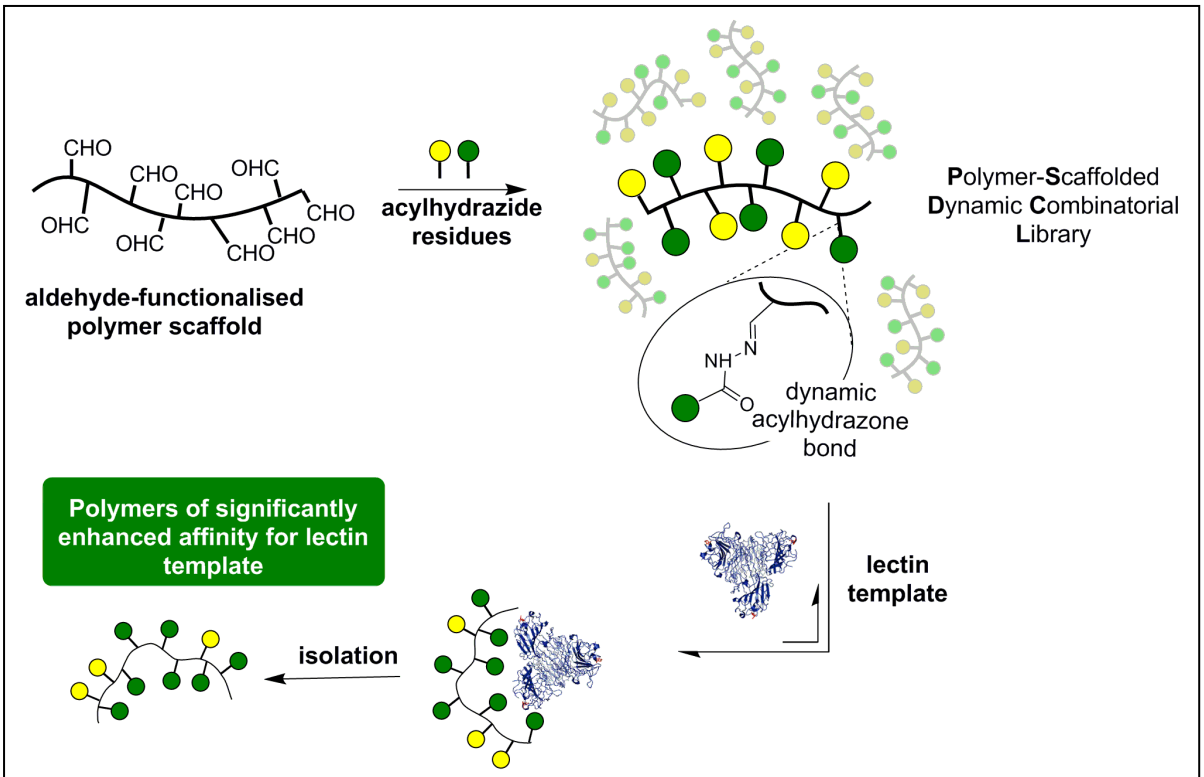

Figure 1: Dynamic combinatorial chemistry on an aldehyde-functionalised polymer backbone with galactose (yellow circle) and mannose (green circle) sugar hydrazides. Figure is adapted from Mahon *et al.,* (2015) *Org. Biomol. Chem.* **13**, 2756-2761.

In some of our studies we aim to make molecules that are precisely tailored to match the valency of the target carbohydrate-binding protein (lectin). For example, we have made inhibitors of the pentavalent cholera toxin protein by attaching five copies of the natural carbohydrate ligand onto pentavalent scaffolds based on dendrimers and bacterial toxin proteins. However, we have also recently been investigating if we can use dynamic combinatorial chemistry on polymers to allow the inhibitor to optimise its own binding to the target protein. In this approach, a polymer bearing aldehyde groups is allowed to react with different carbohydrates that have hydrazide functional groups. Around pH 4-5 the resulting hydrazone formation is reversible and the sugar ligands that prefer to bind to the protein become incorporated selectively into the polymer chains to create the most active multivalent inhibitors.

Publications

Fu O., Pukin A.V., Van Ufford H.C.Q., Branson T.R., Thies-Weesie D.M.E., Turnbull W.B., Visser G.M. & Pieters R.J. (2015) Tetra-versus pentavalent inhibitors of cholera toxin. *ChemistryOpen* **4**:471-477.

Mahon C.S., Fascione M.A., Sakonsinsiri C., Mcallister T.E., Turnbull W.B. & Fulton D.A. (2015) Templating carbohydrate-functionalised polymer-scaffolded dynamic combinatorial libraries with lectins. *Org. Biomol. Chem.* **13**:2756-2761.

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Collaborators

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