

***Searching for Molecular Solutions* – Additional Material**

CHAPTER 8

These Files contain additional material relevant to **Chapter 8** of *Searching for Molecular Solutions*. The page numbers of the book pertaining to each section are shown in the Table below, the corresponding page number for this file, and the title of each relevant section.

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Section A13: *DNA-Templated Synthesis Reaction Discovery*

Relevant to p. 309 of *Searching for Molecular Solutions*, with respect to the general DNA-templated synthesis discussion.

DNA-templated synthesis has also been successfully applied towards chemical reaction discovery ¹, as portrayed in simplified form in Fig. 7A13.1.

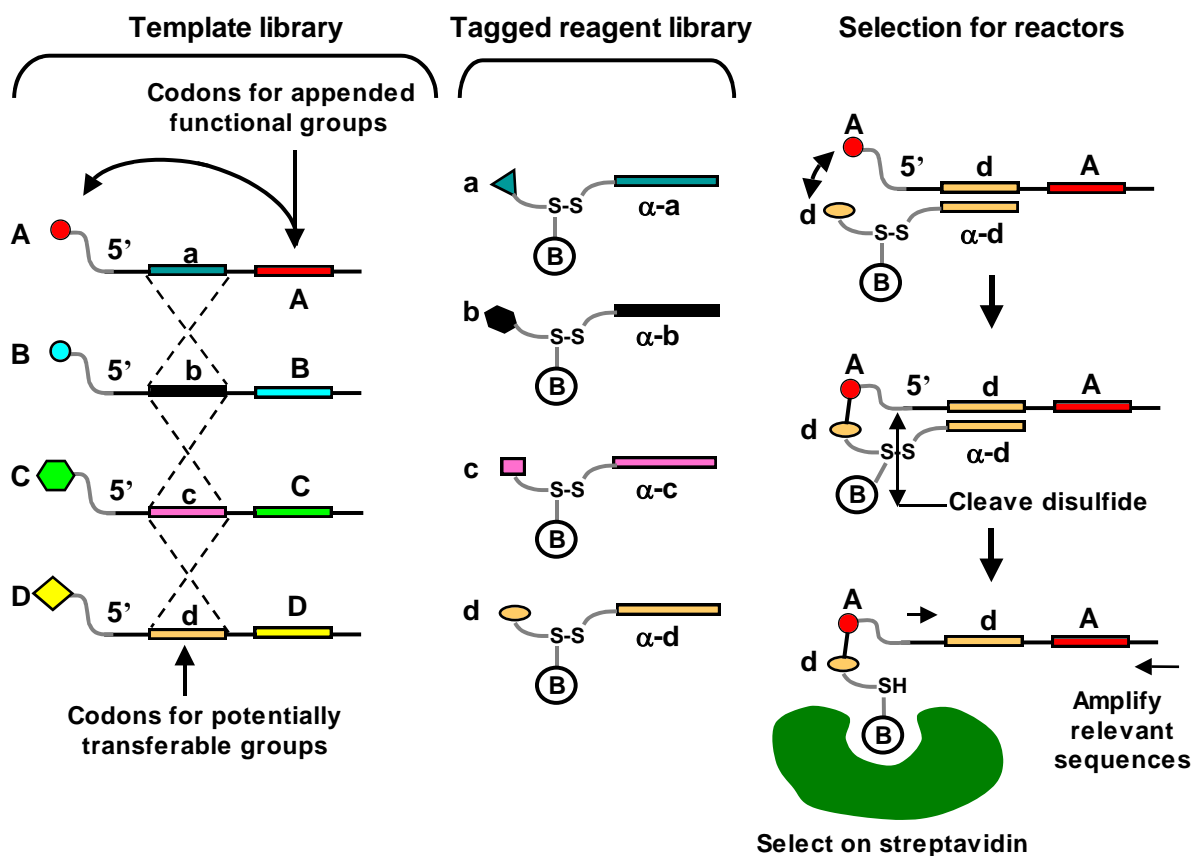


Fig. 7A13.1

Fig. 7A13.1. Application of DNA-templated synthesis for chemical reaction discovery. Template strands contain tags to encode their own functional group attachments and ‘codons’ for a reagent library with a special disulfide-biotin tag as shown and matched for colors, and ‘anticodons’ complementary to codons on the template strands. (indicated as ‘ α -a’ for sequence complementary to ‘a’ codon, etc.) All combinations of reagent library codons are present in the template strands, as indicated by cross-over dotted lines. Pairs of functional groups which are capable of reaction and bond formation allow the biotin group to be effectively transferred to the template strand which encodes both compounds, after disulfide cleavage (reduction). (All other biotin groups on unreacted reagent library members are cleaved from their appended DNA tags). Selection for biotin binding on solid-phase streptavidin allows amplification of candidate reactive pairs.

One limitation of synthesis directed by DNA templates is hybridization itself, since reaction conditions which destabilize DNA:DNA hybrids will by definition hinder the process. This problem does not arise when chemistries are tailored to direct coupling of reactants to modified DNA ends, as in the DNA display scheme of Fig. 8.11 in *Searching for Molecular Solutions*, but it is not yet clear what range of reactions will be fully amenable with DNA display for robust encoded library formation². Two strategies have been used to overcome the hybridization limitation of DNA-templated synthesis and thereby extend its practical utility. When direct conjugation of a reagent with DNA is impractical, in some cases it is possible to use a precursor molecule for such DNA coupling, followed by transformation of the appended moiety to the desired state by means of a specific DNA-templated synthesis reaction. The aim of such an exercise is to produce modified functional groups which can react with other reagents directly under conditions incompatible with duplex stability, while retaining an informational DNA tag³. Alternatively, appropriate enzymatic manipulations can allow incorporation of nucleobases with appended functional groups of interest into single-stranded DNA where the local sequence context is designed to encode the conjugate molecule of interest. Combinatorial co-attachment of a single strand bearing a disulfide-biotin selection module (in a similar

configuration to that shown in Fig. 7A13.1; with another appended functional group) allows encoded chemical reactivities to be selected under conditions incompatible with nucleic acid hybridization⁴.

References:

1. Kanan, M. W., Rozenman, M. M., Sakurai, K., Snyder, T. M. & Liu, D. R. Reaction discovery enabled by DNA-templated synthesis and in vitro selection. *Nature* **431**, 545-9 (2004).
2. Rozenman, M. M., McNaughton, B. R. & Liu, D. R. Solving chemical problems through the application of evolutionary principles. *Curr Opin Chem Biol* **11**, 259-68 (2007).
3. Sakurai, K., Snyder, T. M. & Liu, D. R. DNA-templated functional group transformations enable sequence-programmed synthesis using small-molecule reagents. *J Am Chem Soc* **127**, 1660-1 (2005).
4. Rozenman, M. M., Kanan, M. W. & Liu, D. R. Development and initial application of a hybridization-independent, DNA-encoded reaction discovery system compatible with organic solvents. *J Am Chem Soc* **129**, 14933-8 (2007).