

3.4

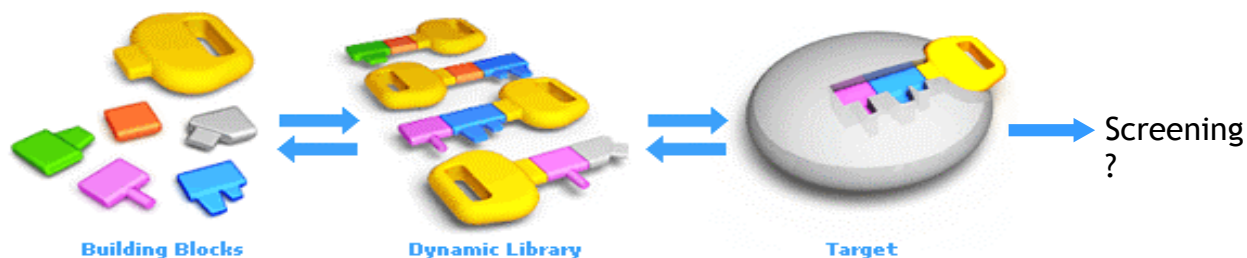
SCREENING OF DYNAMIC COMBINATORIAL LIBRARIES USING FOURIER TRANSFORM ION CYCLOTRON RESONANCE MASS SPECTROMETRY

Poulsen, Sally-Ann
Eskitis Institute, Griffith University, Brisbane Q 4111.

The rapid discovery of novel proteins, often with unknown function, has challenged medicinal chemistry to digress from a target-based to a diversity-based approach to small molecule chemical synthesis. Dynamic combinatorial chemistry (DCC) is a diversity-based approach to chemical synthesis. Our research program aims to refine DCC into an effective drug discovery tool, by integrating DCL generation with screening.

Dynamic combinatorial libraries (DCLs) contain molecules that are generated from a set of building blocks, the connections between which are *reversible*. DCLs can change composition in the presence a target protein by shifting the equilibrium to increase the concentration of the DCL member(s) that best recognises (through molecular recognition) the guest. DCC proceeds not to generate high yielding pure compounds, as is most often the desired outcome of conventional synthesis, but rather to access diversity and exploit the effective amplification of the 'best binder' by the addition of a suitable (protein) target in a screening protocol, Scheme 1.

Scheme 1: Dynamic combinatorial chemistry in the presence of a target.¹⁻³



This presentation will describe an investigation into mass spectrometry as a means of screening DCLs to identify the 'best binders' without the need for solution phase separation or complex deconvolution strategies. Specifically, the methodology to be presented will describe the use of ESI FTICR MS to trap and isolate noncovalent complexes between a protein target and small molecule binder(s) from a DCL and the subsequent identification of the small molecule(s).

A. V. Eliseev et al. Target-induced formation of neuraminidase inhibitors from in vitro virtual combinatorial libraries, *PNAS* **2002**, *99*, 3382-3387.

J. -M. Lehn et al. Dynamic deconvolution of a pre-equilibrated dynamic combinatorial library of acetylcholinesterase inhibitors, *ChemBiochem* **2001**, *2*, 438-444.

J. -M. Lehn et al. 'Dynamic combinatorial carbohydrate libraries: probing the binding site of the Concanavalin A Lectin', *Chem. Eur. J.* 2004, *10*, 1711-1715.