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Realising Activity-Directed Synthesis

The functional and structural diversity of natural products continues to inspire drug discovery and chemical biology. Natural products arise through the evolution of biosynthetic pathways, driven by functional benefit to the host organism (Figure, Panel A). In stark contrast, most other bioactive molecules are discovered through optimisation rounds in which synthesis, purification and assaying are distinct activities. To expedite discovery, a narrow toolkit of reliable methods has emerged, tending to focus attention on a limited range of molecular scaffolds. Current discovery paradigms thus tend to discourage exploitation of the full power of modern synthetic methods.

We have recently described a new discovery approach – which we term activity-directed synthesis (ADS) – in which novel bioactive small molecules emerge in parallel with associated syntheses (Figure, Panel B).^{1,2} Distinctively, ADS harnesses the promiscuity of reactions that can yield alternative products. Although such reactions explore diverse chemical space, they are rarely exploited in current discovery approaches which generally require high-yielding reactions with predictable products. In each round of ADS, a reaction array is performed with outcomes that are critically dependent on the specific substrates/catalysts/conditions used. To steer reactions towards bioactive products, subsequent arrays are informed by the bioactivity of the product mixtures. Finally, reactions that yield highly active product mixtures are scaled up to reveal, after purification, the responsible bioactive structures. Thereby, ADS can enable adventurous and powerful synthetic methods to be exploited in the discovery of bioactive molecules in parallel with associated syntheses.

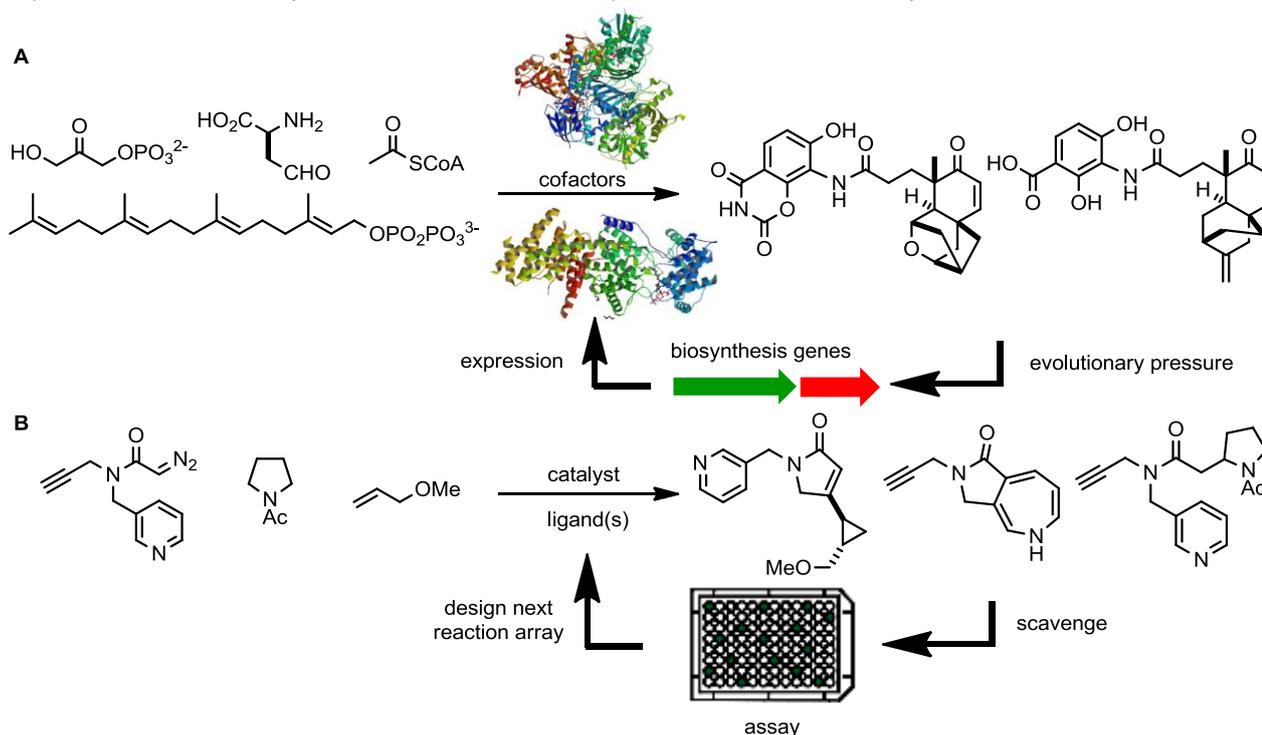


Figure: Approaches in which the emergence of syntheses of bioactive molecules is driven by function.

Panel A: The evolution of biosynthetic pathways is driven by the benefit of natural products to the host organism. Panel B: ADS in which novel bioactive small molecules emerge in parallel with associated synthetic routes.

The project will involve the expansion of the platform of chemical reactions that are configured for ADS, and the exploitation of ADS in the discovery of novel and diverse small molecules with specific biological functions.

References:

⁽¹⁾ G. Karageorgis, S. Warriner and A. Nelson, *Nature Chem.* 2014, **6**, 872. The paper was featured on the front cover of the October 2014 edition, in a web focus on biomimetic drug discovery, and in an editorial (p 841), an interview (p. 845) and a *News & Views* article (p. 851; Lowe).

⁽²⁾ G. Karageorgis, M. Dow, A. Aimon, S. Warriner and A. Nelson, *Angew Chem. Int. Ed.* 2015, **54**, 13538.