UNIFIED APPROACHES FOR THE SYNTHESIS AND ELABORATION OF DISTINCTIVE FRAGMENTS

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Natural products continue to inspire both drug discovery and chemical biology. Natural products are necessarily biologically-relevant because they arise through the evolution of biosynthetic pathways, driven by functional benefit to the host organism. In this lecture, two complementary and unified approaches for the synthesis and elaboration of fragments will be described that have taken some inspiration from natural products and biosynthesis.

First, the design and synthesis of natural product-inspired scaffolds will be described. The scaffolds were designed to have high natural product-likeness, and to be decorated to yield screening compounds with lead-like molecular properties. To demonstrate their biological relevance, a set of fragments has been prepared from the scaffolds, and has been screened against a disparate range of protein targets using high-throughput protein crystallography. It is demonstrated that the fragments can provide distinctive starting points for the discovery of modulators of epigenetic protein targets.

Second, a novel discovery approach – activity-directed synthesis (ADS) – will be described. Unlike traditional medicinal chemistry workflows, ADS deliberately 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 exploit adventurous and powerful synthetic methods in the discovery of bioactive molecules in parallel with associated syntheses. In the context of fragment-based ligand discovery, the approach can enable productive fragment elaboration in the absence of structural information.