## 2nd Anglo-Swiss Symposium
## Basel, Switzerland

# 'Pharmacophore-Directed Retrosynthesis' Applied to Bioactive Natural Product Synthesis and Cellular Target Identification

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The architecture and bioactivity of natural products frequently serves as an embarkation point for exploration of biologically-relevant chemical space. Total synthesis followed by derivative synthesis has historically enabled a deeper understanding of structure-activity relationships. However, synthetic strategies toward a natural product are not always guided by hypotheses regarding minimal structural features required for bioactivity *i.e.* the pharmacophore. We will present a new approach to natural product total synthesis and probe synthesis that we term 'pharmacophore-directed retrosynthesis'.[1] In this strategy, a hypothesized, pharmacophore of a natural product is selected as an early synthetic target and this dictates the retrosynthetic analysis. In an ideal application, sequential increases in structural complexity of this minimal structure enables development of an SAR profile throughout the course of the total synthesis effort. This approach has the potential to identify simpler congeners retaining bioactivity at a much earlier stage of a synthetic effort along with access to probes for cellular target identification. A few examples of this synthetic strategy contrasted against more traditional approaches will be described.

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