Accessing, Understanding, and Optimizing Natural Products Through Chemical Synthesis

The natural product eupalinilide E promotes expansion of hematopoietic stem and progenitor cells (HSPCs) through a novel mechanism of action. Following our synthesis of eupalinilide E we confirmed the ability of the natural product to drive HSPC expansion and prepared an active tool compound. Using this compound, Eu-probe, we have identified thioredoxin as a target of eupalinilide E that drives HSPC expansion and shown simpler small molecules can lead to the same phenotype in HSPCs derived from human umbilical cord blood.

The natural products vinaxanthone and xanthofulvin promote regeneration in animal models of spinal cord injury and corneal transplant. Through chemical synthesis substantial quantities of both natural products have been accessed enabling the syntheses of chemically edited derivatives. Through the use of microsurgery using laser ablation of axons the growth promoting activities of the analogues could be assessed. In addition, the natural products have been determined to function as positive allosteric modulators of the succinate receptor 1 (SUCNR1) as well as inhibitors of semaphorin 3A.