Marine Natural Products as Starting Points for Drug Discovery and Development

Over half of all current drugs are derived from natural products, while the marine environment represents a largely untapped resource. Natural products from marine cyanobacteria cover therapeutically relevant chemical space. This is underscored by the approval of brentuximab vedotin, an antibody-drug conjugate with a cytotoxic payload that is derived from dolastatin 10 which is produced by the marine cyanobacterium *Caldora penicillata*. In addition to dolastatin 10, we have discovered novel cytotoxins with different mechanisms of action, including novel inhibitors of class I histone deacetylases and of cotranslational translocation. A requisite for the development of these marine natural products into therapeutics is the detailed characterization of their mechanisms of action, along with solving the supply problem. Using orthogonal target-based profiling approaches, we also identified new protease inhibitors and GPCR modulators and linked them to antimetastatic potential and applications for wound healing or treatment of pulmonary diseases. An integrative platform of pharmacological, genomic and proteomic profiling assisted us in understanding their activities on the cellular and molecular level. Total synthesis and medicinal chemistry campaigns for prioritized compounds allowed us to improve selectivity profiles. Rigorous biological evaluation directed us to specific disease indications and enabled us to perform more targeted preclinical studies. In parallel, our genome mining strategies led to the identification and cloning of selected biosynthetic gene clusters for subsequent heterologous expression as a complementary approach to address the supply problem. Our marine biodiversity-based discovery platform can catalyze the development of novel therapeutics from the ocean.