NATURAL PRODUCTS IN DRUG DISCOVERY FOR IMMUNOTHERAPY

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Natural products represent an important pipeline for new investigational drugs due to their unique chemical diversity. Compounds from plants and microbes have historically been an important source or inspiration of pharmacologically active substances. Systematic research of marine natural products, however, waited for the refinement of technologies until the early 1960s, even if the pharmaceutical potential of marine organisms soon became clear when Werner Bergmann reported the unusual sponge nucleosides that eventually led to development of the antiviral and anticancer drugs ara-A (vidarabine) and ara-C (cytarabine) used clinically for decades.[1,2] Modern NMR and mass spectrometry approaches marked the golden age of the field and were crucial between the 1970s and 1980s for the identification of thousands of secondary metabolites with complex carbon skeletons, often very different from their terrestrial counterparts, and new bioactivities based on previously unknown modes of action.[3] However, only the advent of cellular and molecular techniques in the new century has finally paid off with the approval as new therapeutic agents of Ziconotide (ω-conotoxin MVIIA) and Trabectedin (ecteinascidin-743), the two complex molecules derived from marine organisms.[4,5]

Drug discovery is the process by which new candidate drugs are searched for. In the early phase (lead or hit discovery) the process concerns the identification and validation of candidate molecules that evoke a biological effect. In immunotherapy, which is the use of immunity-enhancing approaches as a medical treatment, the aim is the discovery of molecules that can trigger an inducible response *to eliminate infections and damaged self-cells, and maintain physiological homeostasis and health*. The presentation will report the results of recent studies on the unconventional modulation of innate immunity by natural products in my laboratory. I will discuss the strategies for the search for novel drug candidates for anti-cancer and immunotherapeutic treatments, and focus on the case of a class of marine sulfolipids, e.g. Sulfavant A (SULF A), that can stimulate cells including phagocytes and antigen presenting cells via mechanisms involving the triggering receptor expressed on myeloid cells 2 (TREM2).[6-8] Using these molecules, we have developed new drug candidates able to potentiate the protective effects of vaccines by stimulation of dendritic cells (DC) or to activate microglia in order to enhance the removal of amyloid beta (Aβ) and slow cognitive and functional decline in Alzheimer's disease.

Key words: *natural products, innate immunity, adjuvant, cancer, neurodegeneration*

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