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Mining Bacteria-derived human host cell signaling modulators for targeted drug discovery

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ABSTRACT

Historically, drug discovery efforts centered on natural products in the Philippines have focused on bioactivity screens of extracts and compounds from terrestrial plants, marine macro-, and microorganisms. While a number of important drugs in the market were discovered using this approach, it entails extremely massive screening operations that are often disproportionate to discovering a commercially viable product. Further, the molecular target is often identified at a much later stage of drug development, and typically done elsewhere. We aim to galvanize drug discovery efforts in the Philippines in two ways. First, we will focus on compounds produced by intracellular bacteria as a source of bioactive molecules. While these bacteria retain the capacity to modulate specific host biological pathways, they have minimized their genome size, reducing the complexity of the search to find bioactive molecules; Second, we will capitalize on specific host signaling pathways that are modulated by these intracellular bacteria, permitting a highly focused search to isolate and characterize bacterial factors that can modulate specific molecular targets. The rationale of this approach is that humans have co-evolved with many microorganisms; therefore, there is an evolutionary pressure for bacteria to be equipped with adequate mechanisms to succeed in establishing their coexistence with their hosts. This includes mechanisms of bacteria-mediated inhibition of human host cell signaling pathways. Because some important diseases result from the hyper-activation of some cell signaling events, we hypothesize that interventions based on known mechanisms employed by microorganisms on the same pathway can be utilized as bases for targeted drug discovery. Therefore, during the first phase of the project we will focus on, Chlamydia trachomatis, an obligate intracellular bacterium, which infects the columnar epithelial cells of the conjunctiva and the urogenital tract. Chlamydia survival is intimately linked to host cell biology. This bacterium is equipped with an arsenal of effector proteins that allows it to modulate many of the host cell signaling machineries that result in the inhibition of apoptosis; inhibition of NFkB signaling; and inhibition of activated STAT1 nuclear translocation. The latter is a recent finding by the proponents of this study that will be exploited to isolate and characterize the chlamydial effector molecule that mediates the inhibition of STAT1 activity. The JAK/STAT signaling pathway plays an important role in chronic inflammatory diseases. Further, strong evidences also suggest that it promotes the development of radiotherapy-resistant cancer cell population. Altogether, these appreciate the value of inhibitors of STAT1 function, as they can be exploited as anti-inflammatory and anti-cancer therapies. In broad terms, this study aims to discover an anti-inflammatory drug candidate that has application in cancer therapy by mining Chlamydia trachomatis effector molecules. The long-term goal of our study is to add to current efforts in natural product-based research by introducing the use of sources that have co-evolved with the human host. Importantly, our study will provide an innovative alternative platform for drug discovery, utilizing an untapped source of bioactive molecules with a smaller search space.

KEYWORDS: Drug Discovery; Bacterial effector molecules; Cancer