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Mining Bacteria-Derived Human Host Cell Signaling Modulators for Targeted Drug Discovery

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Washington State University (WSU)

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Anti-cancer drug discovery

Cancer is one of the leading causes of morbidity and mortality in the Philippines. In 2010 alone, it was estimated that 82,468 individuals were diagnosed to have cancer for the first time. Furthermore, in the same year, nearly 52,000 Filipinos died of malignancies. Because of the very high mortality rate, cancer is one of the priorities of the Department of Health (DOH).

Available cancer treatment regimens in the country are imported products not affordable to the majority of indigent Filipinos, such as fludarabine, a purine analog that targets signal transducer and activator of transcription 1 (STAT1) function. However, its anti-cancer activity relies primarily on its cytotoxicity. Therefore, like most anti-cancer drugs, it can cause immediate side effects like nausea and alopecia.



Several anti-cancer drug discovery efforts in the Philippines focus on the development of natural products from extracts developed from bioactivity screens and compounds from terrestrial plants and marine macro- and microorganisms. However, this process entails extremely massive screening operations often disproportionate to the discovery of a commercially viable product. Furthermore, the molecular target is often identified at a much later stage of drug development and typically is not done in the Philippines.

HCT116 cell line being propagated and used in experiments for this project

To reduce complexity in the search of bioactive molecules that would potentially make anti-cancer treatment affordable, UPD, with support from USAID STRIDE, embarked on anti-cancer drug discovery involving compounds produced by intracellular bacteria that will modulate specific host biological pathways resulting to genome reduction in microbial genomes. The research capitalizes on specific host signaling pathways that will modulate intracellular bacteria to isolate and characterize bacterial effector molecules. Since microorganisms have co-evolved with human beings, this research expects to capitalize on finding bacterial mechanisms for establishing their coexistence with their hosts.

Milestones

In view of the main objective of the research, which uses the intracellular bacterium *Chlamydia trachomatis* as the main source of the bioactive molecule to target the human host cell signaling pathway, the project has achieved the following:

- Creation of a cell culture laboratory at the Institute of Biology;
- Creation of a bioinformatics protocol for establishment of a chlamydial effector protein expression vector library;
- Analysis of Chlamydial T3SS effector protein for internal restriction of enzymes that will aid in designing primers to be utilized in experiments being conducted;
- Publication of 3 manuscripts: a) *Chlamydia trachomatis* evades the host interferon gamma response during primary infection by targeting the nuclear importin karyopherin α 1; b) Does IFN-gamma act as a molecular switch for *Chlamydia trachomatis*' susceptibility to natural killer (NK) cells and cluster of differentiation 8 (CD8) + T cells?; and c) Probiotic *Lactobacillus* spp. cell-based therapy may target the natural tryptophan salvage reactivation pathway of persistent *Chlamydia trachomatis* in the female reproductive tract;
- Development of a screening assay for the 96-well culture plate format, resulting in a reduction in the working volume of primary antibodies to 0.025 ml; and
- Optimization of the polymerase chain reaction experiments using CT649, a set of synthesized primers with projected amplicon of 972 bp.

These milestones are expected to improve novel approaches of drug discovery. In the long run, they will boost demand and acceptability of natural anti-cancer products worldwide, and thus boost the country's economy through the biomedical and pharmaceutical industries.