Project Title: Towards repurposing existing antiretroviral drugs as anticancer agents for cancer therapy
Grant Awarded: $65,000
Principal Investigator: Dr Danny Rangasamy, John Curtin School of Medical Research, The Australian National University.

The novel hypothesis being tested in this study is that activation of the normally repressed L1 retrotransposons at the early stages of breast cancer triggers or accelerates the invasive behavior of cancer cells by re-programming the expression of genes and non-coding RNAs. To test this hypothesis we treated breast cancer cells with existing anti-HIV drugs, Efavirenz and SPV121, that can inhibit the activity of L1-encoded reverse transcriptase enzyme, thereby blocking the function of L1 retrotransposons. Research work on this project has been very productive. We identified the following findings that will have direct impact on the translation of this research into a preclinical trial of breast cancer patients in the ACT and SE NSW regions.

RESULTS AND PUBLICATION OUTCOMES

1. Our findings show that L1-encoded reverse-transcriptase enzyme and key breast cancer stem cell marker CD44 are highly expressed in almost all human breast cancer tissues. By blocking the activity of L1 retrotrans posons using an existing anti-HIV drugs such as Efavirenz and SPV121 can prevent the formation of self-renewing breast cancer stem cells that are often resistant to chemotherapy and radiation. Thus, this would reduce the risk of cancer recurrence and distant metastases.
2. Our studies show that Efavirenz and SPV121 drugs can reverse the migratory and invasive properties of breast cancer cells that enable the cancer cells spread to distant sites. We have carried out extensive cellular analysis of the cell-cell adhesions and changes in the morphological phenotypes of breast cancer cells with or without drug treatment. These studies show that the majority of cancer cells displayed elongated micro tubule extensions that adhered tightly to their substrate rather the loss of cell-to cell adhesions. Importantly, these morphological changes were reversible upon cessation of drug treatment. These observations further show the importance of targeting L1 retrotransposons for breast cancer therapy.
3. We have also carried out assays to measure the inhibitory effects of Efavirenz and SPV121 drugs on cancer cell growth and toxicological effect of drugs in a wide range of cancer cells ranging from normal cells to breast cancer cells with increasing malignant and invasive behaviors. These included triple-negative breast cancer cells that are hard to treat currently. Our findings show that Efavirenz can induce cell differentiation like a normal cell and trigger cell death (or apoptosis) in breast cancer cells. Notably, we have found that the cancer cell-killing effect of Efavirenz is equivalent to that of novel SPV121 drug, with marked cell killing at a dose of 20 μM.
4. Our transcriptome analysis shows a direct functional link between L1 expression and deregulation of several tumor-supressing miRNAs and in particular let-7 miRNA family, a key miRNA known to target many oncogenes and its expression is hallmark of cell differentiation. Strikingly, our studies show the importance of restoration of let-7 expression, where its expression is lost in breast cancer. This study also allowed us to propose a new therapeutic option for the treatment of breast cancers by inhibiting L1 activity using existing Efavirenz and SPV121 drugs.

DIRECT PUBLICATIONS FROM THIS PROJECT

1. Rangasamy D, Lenka N, Ohms S, Dahlstrom JE, Blackburn AC, Board PG. Activation of LINE-1 Retrotransposon increases the Risk of Epithelial-Mesenchymal Transition and Metastasis in Epithelial cancer. Current Molecular Medicine 2015; 15(7): 588-597.

2. Ohms S, Peggy C, Dahlstrom JE, Rangasamy D. Inhibition of LINE-1 Retrotransposon by antiretroviral drugs modulates the expression of miRNAs and genes involved in breast cancer formation. Oncogene 2016.

This study was recently submitted for publication in Oncogene but reviewers required additional experiments for publication. We are in the process of submitting the revised manuscript and hope to get it published shortly.