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Mathematical modelling for CTCE-9908 (a CXCR4 inhibitor) on B16 F10 melanoma cell proliferation

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Melanoma, resulting from the mutation of pigment-producing cells, namely melanocytes, is an aggressive malignancy and remains a major cause of skin cancer mortality. The alarming rise in incidence and mortality demonstrates the urgency for new treatment strategies. Melanoma cells overexpress CXC chemokine receptor 4 (CXCR4), which is a G-protein coupled receptor. CXCR4 is activated upon binding to its cognate chemokine ligand, namely CXCL12, which activates downstream signalling pathways, including the mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase/ protein kinase B (PI3K/AKT), phospholipase C (PLC) and Ras homolog gene member A (RhoA) pathway. The activation of these pathways contributes to melanoma metastasis by promoting tumour cell migration, survival, adhesion and proliferation. A known CXCR4 inhibitor, CTCE-9908 is a peptide analogue of CXCL12. CTCE-9908 contains an altered NH2-terminal sequence and competitively binds to CXCR4. By disrupting receptor phosphorylation, CTCE-9908 previously inhibited cellular responses associated with downstream signalling pathways of the CXCL12/CXCR4 axis and ultimately resulted in decreased migration, adhesion and proliferation levels in several cancers. Uncontrolled cell proliferation in cancer is promoted by impaired cell cycle regulation and deregulated cell death. Therefore, this study aimed to investigate the effects of CTCE-9908 on tumour cell proliferation in B16 F10 melanoma cells in vitro.

Crystal violet staining was used to study the effects of CTCE-9908 on CXCR4 inhibition on tumour cell proliferation and to determine the half-maximal

inhibitory concentration (IC50). Crystal violet (CV) is a triphenylmethane dye that stains the cell nuclei and quantifies cell proliferation, or the cytotoxicity of chemicals, drugs, or toxins on cells. Crystal violet (CV) stains negatively charged molecules such as deoxyribonucleic acid (DNA). Therefore, this method can be used to determine cell proliferation or cell death when cells are introduced to death-inducing agents.

Data derived from CV experiments were used to construct a mathematical model on inhibition of cell proliferation as a function of time (24, 48 and 72 hours) and CTCE-9908 concentration (0-0.051 mM). However, no significant inhibition of cell proliferation was obtained at these conditions, and the CTCE-9908 concentration was therefore increased for experiments at 48 hours (0-0.51 mM). As a result, the mathematical model allows for approximating parameters outside the current dataset and predicting data for the increased CTCE-9908 concentrations at 24 and 72 hours. In addition, the mathematical model was used to predict an IC50 for CTCE-9908 on B16 F10 melanoma cells.

Overall, the mathematical model contributes to the knowledge of CTCE-9908 on inhibition of CXCR4-mediated B16 F10 melanoma cell proliferation and confirms that the compound inhibits the metastatic parameter, namely proliferation at the calculated IC50. CTCE-9908 may offer future treatment strategies in combination with other viable treatments against melanoma. The authors recommend that future research, such as in vivo studies, is necessary to substantiate the findings of this study.

Keywords: melanoma, cell proliferation, mathematical modelling

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