Summary

The results presented in this thesis show that the transformed cells of macrophage lineage such as J774A.1, P388D1 and IC21 take up and degrade a conjugate of the antineoplastic drug, daunomycin (DNM), with maleylated bovine serum albumin (MBSA) with high efficiency and saturation kinetics through the scavenger receptors expressed on the surface of these cells. In contrast, transformed cells of non-macrophage lineage, *viz.*, L929, EL4, Bowes melanoma and CHO do not take up and degrade the drug conjugate, indicating that these cells are scavenger-receptor-deficient. In the conjugated form, about 0.1 μM-DNM causes 50% inhibition in the uptake of ^{3}H-thymidine by the receptor-bearing J774A.1 cells, whereas the receptor-deficient Bowes melanoma cells are not affected. Free DNM (0.1 μM) does not significantly affect the uptake of ^{3}H-thymidine by either cell types. Treatment of cells derived from intraperitoneal tumors induced in BALB/C mice by J774A.1 cells with 0.4 μM DNM in the conjugated form for 5 hours abolished their ability to form tumors. In contrast, transplantation of untreated cells or cells treated with free DNM under identical conditions led to the tumor formation and subsequent death of the mice.

A major obstacle to successful chemotherapy of cancer is the development of resistance to multiple drugs. In order to determine if the drug resistance in the macrophage tumor cells could be circumvented by receptor-mediated drug delivery, a DNM resistant variant of J774A.1 cells was developed by culturing the cells in presence of increasing concentrations of DNM. The resultant cells, named JD-100, also showed

increased resistance to a variety of drugs. The drug resistance phenotype expressed by the JD-100 cells is of a complex type and might involve P-glycoprotein-dependent and independent mechanisms. Our results show that the scavenger receptors on both the cell types are similar in content as well as function. MBSA-DNM effectively inhibited ^{3}H-thymidine incorporation by JD-100 cells at a relatively low concentration(0.3 μM). In contrast, the same concentration of drug in the free form did not elicit any cytotoxic effect.

Finally, studies were carried out to determine the antitumor efficacy of the drug conjugate using macrophage tumors in BALB/C mice as a model system. In these studies, the drug conjugate suppressed the growth of subcutaneous tumor in the BALB/C mice at much lower dosages of DNM relative to the free form of the drug. Thus, 50% reduction of the tumor mass was elicited by 0.7 μg of DNM in the conjugated form whereas about 28 μg of the drug in the free form was necessary to achieve similar antitumor effect. It was also found in this study that MBSA-DNM treated tumor bearing mice survived throughout the experimental period of 230 days. In contrast, free drug at a similar concentration did not significantly suppress the tumor growth and all the animals died within 30-40 days. These findings merit serious consideration in the development of new chemotherapeutic agents for the treatment of histiocytic malignancies which involve cells of macrophage lineage bearing the scavenger receptors.

In conclusion, these results show that effective delivery of drugs to macrophages can be achieved by scavenger receptor mediated endocytic pathway to eliminate the cancer cells which express these receptors. This methodology is of a general nature and might be used for delivering a variety of anticancer agents. It may also be possible to specifically activate the antitumor properties of macrophages by delivering immunomodulators using this methodology.