Chapter 1

Introduction

The spectacular success of chemotherapy in controlling infectious diseases in this century is largely due to the availability of various drug substances which differentially affect the host and the invading pathogens. This approach, first conceptualised in 1906 by Ehrlich (1), has worked well when unique differences between the normal and diseased states of the host could be distinguished. In diseases such as cancer, however, the differential sensitivity of normal and neoplastic cells to currently available anticancer drugs is relatively small and toxic side reactions severely limit the utility of many anticancer drugs. The adverse side reactions to drugs presumably arise due to the fact that at therapeutically effective concentrations in the blood, the non-target cells in the body are also exposed to the cytotoxic effects of the drug. Therefore, targeting of drugs selectively to the cells where the pharmacological action is desired is expected to increase their therapeutic efficacy as well as decrease the toxic side effects resulting from the interaction of the drugs with the normal cells.

One approach to achieve site-specific drug delivery consists of linking of a cytotoxic agent to a carrier which is recognised by a specific determinant present on the surface of target cells. Ideally, a successful drug-carrier complex should fulfil several essential criteria, namely, a) it should be able to cross anatomical barriers to reach the target tissues, b) the carrier should be recognised by specific determinants present on the surface of the target cells, c) the linkage between the cytotoxic agent and the carrier should be biodegradable inside the cells but stable in the circulation, d) the conjugate
should be nonimmunogenic, e) the conjugate should be amenable to manufacture under sterile and apyrogenic conditions, f) the conjugate should have long shelf life. Various carriers like antibodies, liposomes, DNA, glycoproteins etc. have been used to achieve this goal. The literature on the subject is vast and several comprehensive recent reviews and monographs are available (2-5).

In the present thesis, we have sought to establish the feasibility of delivering drugs to cancer cells of macrophage lineage exploiting the exquisite specificity and high efficiency of the process of receptor-mediated endocytosis. Our approach consists of linking of an appropriate antineoplastic drug to a macromolecular carrier recognised by an endocytic receptor system present exclusively on the surface of macrophage cancer cells. Such a drug conjugate should bind to the receptors with high affinity, leading to internalization and subsequent degradation of the ligand in the lysosomes. Therefore, it is likely that if drugs are coupled to an appropriate carrier, the drug will be delivered intracellularly following degradation of the carrier.