CURRENT STRATEGIES IN TUMOR-TARGETING

Chapter XVI

Walter Mier\(^1\)*, Johannes Hoffend\(^1\), Uwe Haberkorn\(^1\)
and Michael Eisenhut\(^2\)

1. INTRODUCTION

The recent advances in assay and instrument technologies have provided the means for the high throughput screening of large numbers of compounds (Lam, 1997, Cox et al., 1997). These techniques have accelerated the discovery of potent drugs. However, the standard screening methods identify compounds depending on factors such as potency of an enzyme inhibitor or the binding affinity of a receptor ligand. Other factors such as solubility and hydrophobicity, and in particular pharmacokinetics are not sufficiently considered when choosing novel pharmaceutical leads. Regardless of their \textit{in vitro} performance, the success of novel therapeutics is doomed if pharmacokinetics are not considered in the early stages of drug design. To bridge the gap between \textit{in vitro} and \textit{in vivo} drug development, it is suggested to consider tissue specific mechanisms of either drug delivery or drug release. In order to advance the design of novel drugs that target apoptotic pathways, this chapter will introduce the basic principles of drug targeting as they have evolved to date.

The term "chemotherapy" was coined by Paul Ehrlich at the end of the 19th century for the treatment of infectious diseases. From the second half of the twentieth century the linguistic usage of "chemotherapy" was extended to comprise of anti-neoplastic therapies. The first observations of anti-neoplastic effects came from animal experiments and subsequently from the chemical warfare agent mustard gas. In world-war II bone marrow aplasia was observed in American soldiers who were exposed to mustard gas. This led to therapy attempts with derivatives of this agent in patients with malignant hematological diseases (deVita, 1978). In the 40's the antineoplastic effect of folic acid...
antagonists was discovered. In 1948 Farber reported the first remission of an acute lymphatic leukemia after administration of the folic acid antagonist aminopterin (Farber et al., 1949). In the 60's it became clear that some forms of leukemia, particularly those of infancy can be healed by chemotherapy (Laszlo, 1995). Unfortunately, the hope of healing all cancers by chemotherapy was followed by disillusionment due to the exceedingly slow progress in drug development. Despite the immense progress of cancer research in the areas of tumor development and diagnostics, only few tumors (e.g. acute lymphatic leukemia) can presently be cured, and the vast majority of cancers remain incurable.

The chemotherapeutic agents used in systemic cancer therapy exert their effect mainly on proliferating cells so that not only tumors, but also normal tissue that is physiologically proliferating, such as bone marrow, intestinal or dermal epithelia is affected. Consequently, the systemic side effects of chemotherapeutic agents in healthy tissues represent one of the foremost problems in cancer chemotherapy. These side effects of chemotherapy limit dosing, i.e. drug plasma levels, and compliance of patient's during therapy. Drug targeting which pinpoints tumors specifically, holds the potential of reducing the systemic toxicity of chemotherapy. Unfortunately, most of the currently used chemotherapeutics are not selectively delivered into their target tissues.

In 1906 Paul Ehrlich introduced the expression “magic bullet” (Ehrlich, 1906) for the search of optimized treatment strategies. Since then, research in the sense of drug targeting has focused on the development of carrier systems that increase the therapeutic concentration of a drug in target tissue such as tumors or pathogens thus lowering the side effects of the organism (Gregoriadis, 1977). Ideally, drug targeting should fulfill the following criteria:

• exclusive transfer of the drug to the required site of action
• a minimum of toxic effects for the remaining organism
• use of a pharmacologically inactive vector

In order to carry a drug to a tumor, different strategies are pursued. These are for example, using prodrugs, from which the pharmacologically active part is released in the target tissue by tissue-specific enzymes. A further possibility is to couple effective, non-tissue-specific drugs to tissue-specific, but pharmacologically inert carrier systems like receptor affine peptides or colloidal particles. In the following section the most important drug targeting concepts are presented.

2. LOCAL RELEASE FROM PRODRUGS

The assumption that tumors possess metabolic pathways differing from those found in normal tissues is the basis for the so-called prodrug monotherapy. If for example a

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1 Loco-regional therapy is an alternative to systemic drug targeting. In loco-regional therapy the drug is brought as near as possible to the tumor in order to achieve a high regional concentration and to thus decrease the systemic toxicity. Examples are the intravascular application, (e.g. isolated perfusion, by which the organ concerned is isolated from the remainder of the circulation and perfused with blood and cytostatics) and the intracavitary application, where the drug is given e.g. intraperitoneal, intrapericardial or intravesicular so that little active substance can escape into circulation. The direct application of cytostatic drugs into the vessels supplying the tumor represents the simplest case of loco-regional therapy.