molecular pharmaceutics

editorial

The Optimal Strategy for Drug Targeting

The president of a major pharmaceutical company told me last month that >60% of all drugs will be targeted in less than two decades. The following question then naturally arose: what constitutes a targeted drug? My response was that two major categories of targeted drugs could conceivably be identified. First, drugs that selectively alter an enzyme or pathway uniquely required for the pathology of the "sick" cell can be considered targeted if they do not alter or damage the function of healthy cells. The emergence of data suggesting that a large fraction of cancers may depend on the activities of fusion proteins generated by gene translocations during malignant transformation suggests that many such enzyme targets may exist [Tomlins, S. A.; et al. *Nature* **2007**, *448*, 595–599]. Second, drugs that show no specificity for pathologic cells can also be termed targeted if they are linked to a ligand that forces their selective uptake by the disease-causing cells. An example of the former class of targeted drugs would be imatinib (Gleevec), since it shows specificity for the transforming gene product expressed in only chronic myelogenous leukemia, i.e., the bcr-abl fusion protein tyrosine kinase. An example of the latter class of targeted drugs is EC145, a folate-derivatized construct containing a highly toxic but nonspecific warhead (desacetylvinblastine hydrazide) that in nontargeted form has proven to be too toxic to survive phase 1 clinical trials, but when targeted with folic acid has advanced to a phase 2 clinical trial with a record of low toxicity. Because the receptor for its targeting ligand (i.e., the folate receptor) is primarily expressed on cancer cells, activated macrophages and kidneys, collateral toxicities to healthy tissues have proven minimal.

While a superficial analysis might suggest that the two targeting strategies described above should solve all toxicity problems, experience with each category of targeted drugs argues otherwise. Thus, few cancer-causing proteins are as restricted to malignant cells as bcr-abl. Vascular endothelial growth factor receptor (VEGF-R), epidermal growth factor receptor (EGF-R), matrix metalloproteinases, etc. (i.e., popular choices of many drug-targeting chemists in the field of oncology), all have essential functions outside the proliferation and survival of cancer cells. Similarly, folic acid, LHRH, vitamin B_{12}, and transferrin (i.e., popular ligands for targeting nonspecific drugs to cancer cells) also have receptors on important nonmalignant cells. While use of either strategy alone for drug targeting constitutes a major advance over administration of nontargeted drugs, room for development of drugs with even greater selectivity for pathologic cells still exists.

How might this improved specificity eventually be realized? Three strategies come to mind: (1) identify and inhibit more enzymes and/or pathways uniquely essential to pathologic cells (like bcr-abl is to chronic myelogenous leukemia), (2) combine the selectivities of both targeting strategies in the same molecule to achieve a "supertargeted" drug (e.g., target an EGF-R inhibitor with folic acid to avoid the toxicity to healthy cells of EGF-R inhibitors), and (3) administer multiple drugs, each targeted with a different ligand largely specific for the pathologic cell (i.e., use multiple targeting ligands whose specificities overlap only in their common abilities to target the pathologic cell).

The focus of this issue is to highlight recent advances in the discovery and use of targeting ligands to deliver attached drugs to pathologic cells. The article by Aina and colleagues describes exciting methodologies for identifying novel targeting ligands that would have never been discovered in a search of the literature. The paper by Engel and co-workers reviews the use of peptide hormones to deliver attached drugs selectively to the gynecological cancers that upregulate the respective hormone receptors. Use of a specific peptide hormone (LHRH) to deliver attached drugs to tumor tissues is then taken to new heights in an article by Chandna et al., who attach multiple copies of both a cytotoxic drug and an inhibitor of bcl2 to the same targeting ligand, thereby generating a formulation

10.1021/mp700111w CCC: $37.00

Published on Web 10/01/2007

whose potency significantly exceeds the potency of any of its individual components. The article by Temming et al. then concludes the papers on peptidic targeting ligands by describing the use of an $\alpha_v\beta_3$-targeted auristatin to selectively kill tumor cells and their associated neovasculature. This latter article also examines several obstacles to ligand-targeted drug delivery and elucidates methods for overcoming these obstacles.

In a switch to nonpeptidic ligands, Lu et al. explore optimization of folate-targeted liposomal drug delivery by investigating the roles of various liposomal formulations in maximizing delivery of doxorubicin to folate receptor-expressing acute myelogenous leukemia cells. Use of folate to target attached drugs to malignant cells is then taken to a new level by Leamon and colleagues, who demonstrate the ability to link synergistic cytotoxic warheads (i.e., a vinca alkaloid and mitomycin C) to the same folate, thereby generating a targeted therapeutic agent with extraordinary potency and selectivity. The use of folate to deliver an attached drug is next given a new twist in the article by Lu et al., who describe application of the vitamin in targeting highly immunogenic haptens to tumor cell surfaces, thereby rendering the cells strongly immunogenic and readily recognized by the host's immune system. Finally, the ability of folic acid to also target activated (but not resting) macrophages is exploited by Varghese and co-workers to successfully treat two murine models of systemic lupus erythematosus. This final article is noteworthy not only because it is the only paper dealing with drug targeting to a nonmalignant disease but also because the paper describes the first successful therapy of either model of this debilitating autoimmune syndrome.

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