CORNERSTONE PHARMACEUTICALS

Emulsiphan Nanoparticles Emulsion

Challenges Faced by Chemotherapies and Other Anti-Cancer Agents

Drug delivery remains a formidable challenge in the successful treatment of cancer. Often, less than 1% of the active ingredients in chemotherapies administered to treat tumors ever reach the desired target within cancer cells. The result: Considerable amounts of drug spread to healthy cells and tissue.

The inability to control drug distribution is a major contributor to less-than-desirable outcomes and serious side effects. The ultimate goal in drug delivery: to deliver the drug into the cancer ***cell*** as well as the tumor mass itself. Achieving this goal maximizes the potential of some of the most powerful anti-cancer agents to destroy the epicenter of the cancer cell and improve patient survival. This, in turn, allows for the administration of less drug, rendering treatment much safer.

Technological approaches to achieving this goal fall into two categories: *passive targeting* and *active targeting*. *Passive targeting* capitalizes on the distinct "leaky" vasculature and limited drainage characteristics of solid tumors. Macromolecules introduced into the blood stream pass through the leaky tumor vasculature and enter the tumor mass, thereby accumulating in the tumor as a result of limited drainage.

Unfortunately, however, strategies used to increase the size of the small molecule drugs used to package these drugs into particles often results in their inactivation and/or inhibits their entry into the cancer cells. Furthermore, the drugs associated with passive targeting are also subject to the same physical forces and washout phenomena as other small molecules. As a result, they limit the amount of drug available to enter and kill the tumor cells.

Active targeting involves the use of targeting molecules possessing a specific affinity for a tumor-associated target to carry molecules that have a toxic effect (cytoxic) not just to the tumor mass, but to the tumor cells, as well. In some cases, the targeting molecule itself may be cytotoxic.

The small number of commercially available products associated with tumor cell-specific substances that stimulate an immune response in the body has generally displayed very limited applications, which is primarily due to two factors: (1) The tumor cell targets tend to be highly specific for particular types of tumor cells; and (2) The targeting molecules are generally complex and expensive to produce in commercial quantities.

Many previously developed delivery approaches have required chemical changes to the drug to make it compatible with the delivery technology. Others have helped to make drugs more soluble but do not contribute to more specific delivery. Furthermore, many delivery approaches have complicated manufacturing schemes that are difficult to bring to commercial scale or result in products that have limited shelf-life and therefore, utility. Some delivery approaches even contribute to unwanted side effects.

Products that combine both the passive and active targeting approaches are under active investigation worldwide. These combination products thus far, however, have also suffered from a lack of applicability to diverse tumor types and can incur the dual costs associated with the production of two separate products.

Cornerstone's Solution: Emulsiphan Drug Delivery Platform

Cornerstone's Emulsiphan Drug Delivery System capitalizes on both passive and active targeting approaches.

It is a novel drug-delivery technology that deposits cancer-fighting drugs directly into cancer cells--not just the tumor mass--by focusing on the distinct metabolism of these cells. Just as the body needs nutrients to survive, cancer cells depend on certain nutrients to make energy and to proliferate. Emulsiphan contains nutrients that are attractive to tumors and therefore taken up by them.

The size of the Emulsiphan microscopic particles (nanoparticles) takes advantage of the passive targeting phenomenon and is expected to promote concentration of the drug within solid tumor masses. As Emulsiphan nanoparticles are then internalized within the ***cell***, it is hypothesized that the drugs they contain will be unaffected by the physical forces and washout phenomenon exerted on molecules inside and outside the cell.

As a result, Emulsiphan's passive and active targeting features are expected to increase the amount of drug that reaches the target and decrease the exposure of normal cells to the drug, making the approach safer and more effective.

This form of tumor accumulation and cell uptake is referred to as "active targeting and cellular internalization." By delivering high concentrations of drug directly into malignant cells, Emulsiphan increases the effectiveness and decreases the toxicity of active drugs such as chemotherapies and other anticancer agents. Emulsiphan can also be used to deliver cancer-imaging agents into cancer cells.

Benefits of Emulsiphan:

1. Delivers the active drug not just into tumors, but more importantly, into tumor cells at the site of the drug's intended molecular target, which optimizes the opportunity for efficacy.
2. Since tumor cells preferentially take up Emulsiphan, damage to sensitive healthy cells is reduced, improving drug related side-effect profiles.
3. Can deliver drugs to tumors that are hard for traditional chemotherapies to reach. Even, potentially, hard-to treat-tumor cells such as those of the brain, liver and pancreas are vigorous consumers of Emulsiphan.
4. Requires no chemical change to the drug, allowing for a truncated development pathway of

Emulsiphan-formulated versions of approved drugs.

5. Emulsiphan renders poorly soluble drugs more soluble and stable for prolonged periods of time at room temperature so that they may be packaged in a ready-to-use format without requiring reconstitution at the time of dosing. This is a functional advantage over many existing chemotherapies, since reconstitution can be a potential contributor to errors in drug dosing.
6. Emulsiphan components have been shown to greatly increase the uptake of drug in tumors located in the brains of animals in preclinical testing

EmPAC

Cornerstone's lead Emulsiphan product candidate is EmPAC, a reformulated Paclitaxel product that has demonstrated increased safety and efficacy versus Paclitaxel alone in preclinical testing. Paclitaxel is the active ingredient in one of the most commonly prescribed chemotherapies, Taxol®.

In preclinical testing, EmPAC:

- Delivered a higher concentration of drug delivered to the target at significantly reduced doses.
- Shrunk more tumors and improved survival compared to Taxol alone.
- Demonstrated similar advantages over Abraxane, the only currently approved reformulation of Paclitaxel.

In April 2010, Cornerstone announced a collaboration with the National Cancer Institute (NCI) to develop the combination of certain novel, anticancer agents discovered by NCI with Cornerstone's Emulsiphan Drug Delivery System. EmPAC is in preclinical testing.