

## DRUG DELIVERY THAT OVERCOMES P-GLYCOPROTEIN MEDIATED DRUG EFFLUX

*A drug delivery system that overcomes the problems associated with P-glycoprotein mediated drug efflux.*

### **Disadvantages of Current Treatments:**

P-Glycoprotein (P-gp) is a transport protein that effluxes a wide variety of structurally unrelated drugs out of cells. The bioavailability of various anticancer drugs, anti-HIV drugs, calcium channel drugs, and other drugs which are substrates is limited by this efflux transporter. Over-expression of P-gp by tumor cells confers multi-drug resistance. Efflux of many anticancer drugs including taxol, vincristine, vinblastine, actinomycin D, colchicines, and daunorubicin, from tumor cells makes P-gp a major barrier to chemotherapy. High expression of this transporter on the blood-brain-barrier (BBB) restricts the entry into the brain of P-gp substrates such as anti-HIV drugs such as ritonavir, saquinavir, nelfinavir, and various anticancer drugs, and thus imposes a major challenge in the treatment of various diseases of the brain.

Expression of the efflux transporter on various body tissues and cells not only influences the in vivo disposition of various therapeutically active drugs, but also greatly influences the drugs' pharmacokinetics. It has been known that inhibition of P-gp by various modulators can lead to improved bioavailability of drugs across the intestines, the kidneys, and the BBB. Various modulators that inhibit P-gp are often co-administered with other bioactive agents to increase bioavailability. However, use of these compounds is limited by their toxicity. To achieve P-gp inhibition, doses that result in high serum concentrations of the toxic inhibitor are required. Although various approaches have been studied to overcome P-gp mediated drug efflux, P-gp remains a major barrier to bioavailability, chemotherapy, and effective permeation of P-gp substrates into the brain and other tissues.

### **Invention Details:**

In response to these troublesome efflux issues, UMKC researchers have developed methods of:

- Converting drugs that are substrates for the P-gp transporter into derivatives not recognized by P-gp as substrates, preferably targeted to and recognized by an influx membrane transporter/receptor (such as a peptide, vitamin or other nutrient transporter). The efflux of such derivatives from cells by the P-gp transporter is thereby eliminated or substantially reduced while their transport into target cells by one or more influx transporters/receptors can be effectively enhanced increasing the bioavailability of bioactive compounds that are P-gp substrates.
- Increasing the concentration of bioactive compounds that are P-gp substrates in sanctuary sites of a mammalian subject.
- Enhancing cellular delivery of bioactive compounds that are P-gp substrates.

### **Suggested Uses:**

For use with various anticancer drugs, anti-HIV drugs, calcium channel drugs, and other drugs which are substrates limited by this efflux transporter.

### **Advantages:**

- Inhibition of P-gp by various modulators can lead to improved bioavailability of drugs across the intestines, the kidneys, and the blood-brain barrier.
- Lower toxicity due to less drugs being administered.

US Patents 7,910,553; 7,214,664

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