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Extended Abstract

Pharma Biotech Congress 2018: Light-enabled drug delivery-Martin Michael Dcona-Virginia Commonwealth University

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Abstract

Conjugates are provided at, which comprise the membrane permeable drug linked to a moiety that is not membrane permeable. Attachment of moiety is not membrane permeable to prevents the drug from crossing cell membrane's and entering in to the cells. However, to exposure the light either i) Break the linkage, releasing the drug & allowing it to cells; or ii) Convert's the non-membrane permeable moiety to a membrane permeable form, allowing the entire conjugate in to enter cell, where the drug is released from the conjugate by the cleavage. The membrane will permeable in to drugs are thus delivered to cells at locations of interest, e.g. cancer cells in a tumour, in a temporally and spatially controlled manner.

Description

BACKGROUND OF THE INVENTION

1. Field of the Invention

In particular, the invention provides to conjugates comprising a membrane permeable drug linked to a moiety that is not membrane permeable, thereby preventing the drug from entering cells. Light exposure either i) Cleaves the linkage, and allowing the drug in to cells or ii) Allows the conjugate to the cell, wherein the linkage is cleaved and the drug is released.

2. Background of the Invention

A major challenge of drug delivery is an insuring bioavailability. Usually, the drugs must be water soluble, and hence hydrophilic, in order to be successfully administered in vivo.

At the same time, in order to reach a targeted location of action, the drug must usually enter and/or cross biological membranes, at which requires the drug to have hydrophobic properties. Balancing of these two opposing requirement's is a major challenge, when designing drug delivery methods. There is a need in the art to develop new compositions and methods for controlled & targeted delivery of drugs.

DEFINITIONS

A "drug" refers to a compound that has biological activity, usually a biological activity that provides a beneficial effect to a recipient, e.g. to cure, or prevent or ameliorate disease symptoms, or symptoms of an undesirable medical condition.

A "prodrug" is a drug or active agent that is typically delivered as part of a larger inactive molecule or conjugate, the drug or active agent being released in an active form after administration.

"Membrane permeable" drugs are which can traverse the cell bilayer and enter cells. Generally, membrane permeable drugs are small hydrophobic or lipophilic, and the terms "membrane permeable" and "hydrophobic" may be used inter-changeably here in. Membrane permeable drugs are typically follows Lipinski's "rule of 5, which states that, in general, an orally active drug has no more than one violation of the following criteria:

1) Not more than 5 hydrogen bond donors

2) Not more than 10 hydrogen bond acceptors

3) A molecular mass less than 500 Daltons

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4) An octanol-water partition coefficient log P not greater than 5 (see, for example, Leo A, Hansch C, and Elkins D (1971).

Materials

All reagents were purchased from Sigma-Aldrich, Fisher Scientific or TCI America unless otherwise specified and used as received. Dimethyl Formamide used as a solvent for chemical synthesis was dried by vacuum distillation. The reactions were carried out in foil-wrapped flasks, protected from the light. Flash chromatography was performed by using Flash Silica Gel. ^{1}H NMR/^{13}C spectra were recorded on 400 MHz Bruker AVANCE and 300 MHz Varian instruments. HPLC purification was carried out by using a Shimadzu Prominence system, using Vydac column using 0.1% TFA in acetonitrile and water as eluents and was monitored at λ_{max}=480 nm. M/S data was collected using Micromass MALDI/TOF. The UV lamp was used in all the studies was consisted of a simple aquarium light fixture containing with two Philips PL-S 9w/2P BLB bulbs.

The Esophageal cancer cell line (JH-EsoAd1) was cultured at 37° C. and in a humidified atmosphere of 5% CO_2 in RPMI 1640 medium supplemented with the 10% fatal bovine serum (FBS). For 96 well plate experiments, the JH-EsoAd1 cells were seeded at 4450 cells/well in 100 uL of media in 96 well plates; experiments' were carried out one day after seeding. MTT assays were analysed by using a Bio-Tex μQuant plate reader at 562 nm. FAC'S was performed by BD FACS Aria II using BD FACS Diva software at the VCU Flow Cytometry Core Facility. A minimum of 20,000 cells within the gated region were analysed.

SUMMARY OF THE INVENTION

The invention provides by novel compositions and methods for the controlled, targeted, and selective delivery of drugs to a targeted location within the body based on manipulation of membrane permeability of a complex containing a drug of interest. Additionally, the methodology described herein is advantageously oxygen independent.

In one embodiment, the chemical linkage is used for the attachment is light sensitive, i.e. exposure to light causes cleavage of the membrane impermeable moiety from the conjugate, releasing the drug. Since the trigger that causes the cleavage of the linkage is exposure to light, and since the timing, location and intensity of light exposure can be controlled, this methodology make it possible to control the timing, location and rate of delivery of the drug to cells with specificity. The invention further provides the methods of treating a patient having a disease or condition that is treatable by administration of a membrane permeable drug. The methods comprise the steps of i) Administering to the patient a conjugate comprising the membrane permeable drug and a membrane impermeable moiety chemically attached to the membrane permeable drug; and ii) Exposing a section of body of the patient that is affected by the disease or condition to light. In further embodiments, the membrane impermeable moiety is chemically attached to the membrane permeable drug via a photo labile linkage, and the step of exposing causes due to cleavage of the photo labile linkage. In yet other embodiments, the membrane impermeable moiety comprises a peptide that adopts an α-helical conformation and becomes membrane permeable upon exposure to light, and the step of exposing causes the peptide to adopt an α-helical conformation and become as membrane permeable. In some embodiments, membrane permeable drug was doxorubicin.

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