A Method to Modulate P-Glycoprotein
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Potential Indications

Background

P-glycoprotein (P-gp) is an efflux transporter protein with a broad substrate spectrum that is expressed in many different cell types that actively pumps foreign substances, including drugs, out of cells. In some cancer cells, P-gp is highly expressed and leads to multi-drug resistance, while P-gp expression in brain endothelial cells makes more challenging drug delivery into the central nervous system.

Delivery of therapeutics into the brain

- The Blood-Brain Barrier (BBB) is necessary to protect the brain and maintain its homeostasis.
- Fewer than 2% of small molecule drugs get across the BBB.
- Large molecule drugs cannot penetrate the BBB at all.

Multidrug Resistant Cancer

- Multidrug resistance (MDR) in tumor cells is the leading cause of chemotherapy treatment failure.
- Resistance to therapy has been correlated to the presence ATP-dependent efflux transporters such as P-gp.
- P-gp acts as an efflux pump for various structurally unrelated anticancer agents.

Technology

A novel method to down-modulate P-glycoprotein (P-gp) in cells using adenosine receptor A2A specific-agonists, such as Lexiscan (regadenoson) and S'-N-ethylcarboxamidoadenosine (NECA).

Advantages of the Technology

- Reversible modulation of P-gp.
- Tunable modulation – dependent on the half-life of adenosine receptor agonists.

Proof of Concept

Experiments in vitro (BBB model)

Western blot analysis depicting P-gp expression in human primary brain endothelial cells treated with Lexiscan or NECA (1μM) for up to 72 hours.

Results: Activation of A2A adenosine receptors potently downregulated P-gp expression in brain endothelial cells.

Results: When A2A adenosine receptors are activated by LEX or NECA, it allows entry of substrate of P-gp such as Rhodamine 123 (Rho123).

Experiments in vivo

Fluorescent microscopy of epirubicin accumulation in the brain of mice treated with Lexiscan or Valspoder, a functional P-gp inhibitor, compared to control (t=15 minutes after treatment).

Results: Accumulation of epirubicin is observed, an anti-cancer chemotherapy drug, when A2A activated by agonists.

Reference