

## **A New Therapeutic Approach for the Modulation of Serum Cholesterol Levels**

### **Background**

Phospholipid Transfer Protein (PLTP) is involved in the reverse transport of cholesterol from peripheral tissues to HDLs. The HDLs are in turn absorbed by scavenger receptor class BI (SR BI) in the liver and secreted into bile acids. Previous studies with transgenic mice that overexpress PLTP showed low serum cholesterol levels while knockout mice lacking PLTP expression on high fat diet revealed high serum cholesterol levels and were more prone to develop atherosclerosis. These studies reveal PLTP to be a useful target for the modulation of cholesterol levels.

**The present invention describes a novel approach to modulate serum cholesterol levels via the regulation of PLTP gene expression by a small molecule such as camptothecin and its derivatives.**

### **Description of the Technology**

It was observed, by DNA micorarray analyses, that certain topoisomerase I inhibiting derivatives of camptothecin induce the expression of PLTP in HepG2 liver cells. Specifically, topotecan and other camptothecin derivatives induced both the expression of PLTP gene as well as the PLTP promoter fused to a luciferase reporter construct transfected into HepG2 liver cells suggesting PLTP regulation to be mediated at the level of transcription. By contrast, inactive derivatives of camptothecin and protoberberines (topoisomerase I and II inhibitor) failed to enhance the expression of PLTP indicating that PLTP induction was specific to camptothecin derivatives. Since camptothecin is cytotoxic to normal cells the constructs and cell lines described herein could be used to design assay systems for screening non-cytotoxic cholesterol lowering agents that can be used in the management of serum cholesterol levels.

### **Advantages**

- Current cholesterol lowering agents have limitations: a) Bile Acid Sequestrants (Cholestyramine and colestipol) -Side effects include constipation and are unpleasant to taste.
- b) HMG-CoA reductase inhibitors or statins
  - most commonly prescribed lipid-lowering agents (Mevacor, Zocor, Pravachol, Lescol and Baycol)
  - Statins when combined with cholestyramine and/or niacin are more effective than when given alone. Side effects include hepatitis and myositis.
  - Statins are ineffective in patients with familial hypercholesterolemia, familial HDL deficiency and Tangier's disease
- c) Nicotinic acid (niacin) -Side effects such as gastric irritability, hyperuricemia, hyperglycemia, flushing and pruritus limits its use -Low patient compliance rates because of side effects
- d) Fibric acid derivatives (genfibrozil and clofibrate in the US and fenofibrate and bezafibrate in Europe) -No effect on LDL levels in type II hyperlipoproteinemia and is associated with certain metabolic problems. -Primarily used to treat

## hypertriglyceridemia

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- Diseases such as Tangier's are characterized by low HDL levels. Thus, increasing PLTP expression is a better therapeutic approach for a disease that currently has no therapeutics.

### **Applications**

- . • For the development of screening assays for non-cytotoxic cholesterol lowering agents that enhance the expression of PLTP
- . • For the development of antibodies to PLTP for use in screening assays for cholesterol lowering agents and for the modulation of PLTP expression
- . • For the development of treatment options for Tangier disease, familial HDL deficiency, and familial hypercholesterolemia
- . • For treating patients that are refractory to other cholesterol lowering agents such as statins, niacins, etc.,
- . • For use in combination therapy with conventional cholesterol lowering agents

### **Deliverables**

- . • HepG2 cell lines containing transfected PLTP constructs
- . • PLTP promoter constructs

### **Patent Status**

- . • United States patent application filed.
- . • Application was published on 11/28/2002 (Publication No.: US-2002-0177205-A1)

### **Licensing Opportunity**

- This technology is available for exclusive license.

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