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AN UPSTREAM APPROACH TO IDENTIFY CHOLESTEROL LOWERING DRUGS

Technology Reference
R201

Keywords
Drug Discovery

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Field
Neurological Sciences

Patent Status
US Patent Pending

Cross Reference
This technology is related to discoveries R030 and R034

This invention is a novel approach to discover new drugs that will lower the body's production of cholesterol; and therefore treat atherosclerosis.

AREAS OF APPLICATION

- Rapid screen for identification of new drug candidates for cholesterol regulation

ADVANTAGES

- Competes with current statin based technologies for lowering cholesterol
- Candidate drugs should not show the side effects of statins
- Dual assay system

THE TECHNOLOGY

Cholesterol is an essential constituent of all animal cells and plasma membranes. Its abundance in cells is tightly controlled. How cells sense and signal the abundance of their cholesterol to regulatory effectors is not well understood. In contrast, much is known about the "downstream" elements through which its biosynthesis, storage as esters, ingestion as low-density lipoproteins and transfer into and out of cells via circulating lipoproteins is carried out.

Our invention may help to identify compounds that will signal the "upstream" sensing system to call for a decrease in cholesterol accumulation. Drugs of this type would reduce total body cholesterol by an entirely new mechanism. Briefly, a diverse library of several thousand small compounds can be applied to human cells in an efficient, economical and sensitive multiwell plate screen. Two novel detection systems, involving sterol-specific probes, have been established to identify drug candidates. These agents can be further examined to verify that they lower the accumulation of cell cholesterol. The converse also seems to be feasible: certain compounds will be found that would cause the cell to accumulate excess cholesterol.

A proof of principle has recently been demonstrated for a candidate compound.

The best drugs in current use (namely, statins) inhibit cholesterol biosynthesis by blocking the production of its precursor, mevalonic acid. However, mevalonic acid is also needed in the synthesis of other important cellular constituents. Our approach may therefore avoid the side effects and other limitations of the long-term use of less specific agents like statins and therefore lead to improved approaches to treat atherosclerosis.

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