Version 2.0

Abstract

Back to Hit List

Grant Number:	1R01GM061905-01
PI Name:	CHANG, GEOFFREY A.
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PI Title:	
Project Title:	CRYSTALLOGRAPHY OF MULTI-DRUG RESISTANT-ABC TRANSPORTERS

Abstract: Multi-drug resistance (mdr) is a very significant health problem that is caused by the over-expression of energy-dependent efflux pumps that transports both drug molecules as well as lipids. An important class of mdr pumps belongs to the family of multi-drug resistance ABC (mdr-ABC) transporters. A goal of this proposal is to ascertain the structural components that are involved in the translocation of drug/lipid molecules through the cell membrane and to understand how mdr-ABC transporters achieve their substrate specificity. An important long-term objective of this proposal is to provide a structural framework for comprehending the general transport mechanisms that confer the multi-drug resistance phenotype for the whole family of mdr-ABC proteins. A high-resolution atomic structure could serve as a model for other highly related ABC transporters such as the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) and the Transporter associated with Antigen Processing (TAP) proteins encoded in the major histocompatibility complex in mammals. Recently, a full-length bacterial mdr-ABC transporter has been produced in large quantity and crystallized. The major goal of this proposal is to determine the high-resolution crystal structure of this protein in order to understand the structural components that underlie its substrate specificity and translocation across the cell membrane. Hence, the molecular structural basis of multi-drug resistance will be elucidated. Mdr-ABC transporters are integral membrane proteins, which presents a formidable challenge for obtaining highly ordered crystals. Due to this difficulty, the first three specific aims of this proposal is focused on determining the x-ray structure of this protein. The objective of the last two specific aims is to ascertain the structural basis for the transport and recognition of substrate across the cell membrane by (1) determining the structure of mdr-ABC transporters bound to substrate and/or ATP and (2) solving the structure of single-site mutants that are defective in substrate transport. The specific aims are: 1. Over-expression and purification of mdr-ABC transporter 2. Crystallization and data collection of mdr-ABC transporter 3. Structure determination and refinement of mdr-ABC transporter 4. Structural studies of mdr-ABC transporter concerning substrate translocation 5. Structural studies concerning substrate recognition by mdr-ABC transporter

Thesaurus Terms:
X ray crystallography, membrane transport protein, multidrug resistance, protein structure
P glycoprotein, bacterial protein, lipid transport, protein structure /function
bioimaging /biomedical imaging, crystallization, protein purification

Institution:	SCRIPPS RESEARCH INSTITUTE 10550 N TORREY PINES RD SAN DIEGO, CA 92037
Fiscal Year:	2000
Department:	
Project Start:	01-SEP-2000
Project End:	30-NOV-2005
ICD:	NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES
IRG:	BBCB