and diagnostics executive at SmithKline Beecham and Gen Trak, as Vice President, and her initial task will be to bring the first blood-based diagnostic test for Alzheimer's disease to the market. Moos hopes that MitoKor's diagnostics operation will be a $150 million dollar business in Alzheimer's alone. Diagnostics will also give MitoKor the opportunity to support a managed care environment. The diagnostic tests will indicate which patients will respond to the therapeutics MitoKor and others are developing, so that patients can be selected to achieve optimal response (not unlike the diagnostic metrics, or 'therametrics' strategy that Chiron has pioneered).

Setting up a combinatorial chemistry department, a task that Moos is greatly experienced in, is not on the cards at the moment. Bob Davis and he think that there are already too many good players in that field: 'If someone is already doing it, and doing it well, there is no sense for MitoKor to do it. ... We are only going to do the things we can have a competitive advantage in. If we can't have a competitive advantage, we'll do it with a partner or get a contract organization to do it for us.' Nonetheless, Walter Moos can still think of some untouched areas in combinatorial chemistry, which he and Davis may one day be tempted to explore.

Henriëtte Willems

Toward effective CF treatment

Described within recent memory as a 'disease in search of ideas' because of the paucity of clues to its cause, our understanding of cystic fibrosis (CF) has come into full bloom in the past decade. This most common genetic disease among the Caucasian population is the result of a mutation in the gene for a membrane protein that normally traverses the apical surface of epithelial cells. This protein, the CF transmembrane conductance regulator or CFTR, is a chloride ion channel. In CF, a mutation of the gene results in the absence or severe reduction of chloride ion transport across the apical surface of epithelial tissues. The loss of chloride ion transport causes a concomitant loss of water movement across the same membrane, leading to abnormal secretions and blockage of secretory ducts of the epithelial-lined airways and exocrine glands.

CFTR gene mutations

Unfortunately, growth in our understanding of CF has yet to be matched with a cure or really effective treatment. Part of the problem is the complexity of the gene mutations that cause the disease. More than 600 different mutation sites on the CFTR gene have been identified; as might be expected, there is a direct correlation between the extent of damage to CFTR function by the various mutations and the severity of the disease. Consequently, CF could be considered to be a complex family of diseases based on the molecular heterogeneity of the genetic defects. However, one specific mutation that leads to the deletion of a phenylalanine residue at position 508 (Δ508 mutation), is responsible for approximately 70% of CF cases, and about 90% of CF patients carry at least one Δ508 allele. The loss of the phenylalanine residue leads to a CFTR protein that is mostly degraded by intracellular proteases before it can be inserted into the plasma membrane.

cAMP can activate mutated protein

In normal conditions, the chloride channel protein is activated by elevation of intracellular cAMP, leading to chloride ion transport. However, the small amount of Δ508 protein that does enter the apical membrane does not respond to activation by cAMP. If a strategy could be found to activate this small amount of membrane-inserted Δ508 CFTR protein, then it is likely that some of the most severe symptoms of the disease would be moderated. Dr Thomas Kelley and coworkers at Case Western Reserve University (Cleveland, OH, USA) and the University of Utah, School of Medicine (Salt Lake City, UT, USA) appear to have found such a strategy. They report that the simultaneous administration of forskolin, an adenylate cyclase activator, and milrinone, an inhibitor of type III cyclic nucleotide phosphodiesterase (a combination found to give a maximum rise in intracellular cAMP), leads to chloride transport through the mutated CFTR channel protein in nasal epithelial cells of a mouse CF model. However, administration of either compound alone was completely ineffective in triggering chloride ion transport [*Proc. Natl. Acad. Sci. U. S. A.* (1997) 94, 2604–2608].

Implications for new cystic fibrosis therapies

The findings of this study are important for several reasons. First, it clearly shows that the most prevalent genetic lesion responsible for CF does not lead to a CFTR protein that is totally unresponsive to activation by cAMP. If the level of cAMP is elevated to extreme levels, then the channel can be activated. Certainly, the systemic elevation of the ubiquitous cAMP signaling molecule to the degree needed in this study to open the CFTR channel would have obvious and widespread adverse effects. However, the results suggest that it may be useful to screen for compounds that will more specifically mimic the effect of cAMP on the Δ508 CFTR protein.

Second, because the life-threatening effects of CF are primarily the result of dysfunction of airway epithelium and the direct accessibility of the airways, the strategy of gross elevation of intracellular cAMP might be utilized by delivering drugs in aerosol form directly to the airways. This strategy would be likely to result in the gross elevation of cAMP in airway epithelial cells without widespread systemic effects. Of course, even when confined to airway epithelial cells, such a strategy may lead to severe and intolerable side effects that would make this mode of treatment undesirable or impossible.

However, the finding that chloride ion transport may be induced from the Δ508 CFTR protein is most encouraging, and it should encourage those with expertise in epithelial biology to come up with novel pharmacological strategies to prize open this important channel.

Robert W. Wallace
fax: +1 212 254 3322
e-mail: RobWallace@NASW.org