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## Antibiotics Show Promise as Therapy for Genetic Disorders

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New research findings involving a tried-and-true antibiotic developed decades ago are pointing the way toward a novel approach for treating genetic disorders in the 21st century, researchers suggest.

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In one recent study, investigators at the University of Alabama at Birmingham (UAB) found evidence that gentamicin treatment enabled cells from patients with Hurler syndrome to override the effects of the mutation underlying the disease (*Hum Mol Genet*. 2001;10:291-299).

Furthermore, a growing body of research by the UAB group and others indicates that drugs such as gentamicin may one day be used to treat a subset of patients with a variety of genetic disorders, such as cystic fibrosis and muscular dystrophy. Although clinical trials testing gentamicin or agents with similar properties are at least a few years off, researchers say that laboratory and animal studies, as well as some pilot studies in human subjects, suggest that the approach is feasible.

### SUPPRESSING NONSENSE

Hurler syndrome is caused by a mutation in the *IDUA* gene, which results in the loss of  $\alpha$ -L-iduronidase. Without this enzyme, glycosaminoglycans accumulate in the lysosomes of various tissues, causing organ damage, mental retardation, and early death.

In about 70% of cases of Hurler syndrome, the problem is caused by a stop or "nonsense" mutation in the *IDUA* gene, which prematurely halts translation of the gene's instructions to create the enzyme, explained UAB microbiologist David Bedwell, PhD. In the new work, Bedwell and colleagues found that cells from such patients showed  $\alpha$ -L-iduronidase activity after treatment with gentamicin.

Gentamicin and some other aminoglycosides "have the capacity to suppress premature stop mutations and allow the ribosome to read past a false-stop signal and get to the appropriate termination signal at the end of the gene," explained John Paul Clancy, MD, of UAB's department of pediatrics. But not all stop mutations are alike—the ability of a particular substance to suppress a stop mutation depends in

part on the identity of the nucleotides surrounding the false stop signal.

In the study of patients with Hurler syndrome, gentamicin suppression of the stop mutation led to restoration of about 3% of normal levels of the enzyme, noted Bedwell. Because milder forms of the disorder suggest that as little as 1% of normal enzyme activity is needed to avoid most of the manifestations of Hurler syndrome, the enzyme levels resulting from gentamicin treatment may be sufficient to allow children with the gene defect to live longer, more normal lives, said Bedwell.

Aminoglycosides such as gentamicin kill bacteria by targeting and binding tightly to the microbes' ribosomal RNA decoding site. Researchers believe that gentamicin binds to the analogous position in the mammalian ribosome, but more weakly—and hence is much less toxic for humans and other mammals than it is for drug-susceptible bacteria.

This treatment for Hurler syndrome, if effective, would be welcomed by clinicians who care for patients with this devastating disease. Bone marrow transplants, a current option, involve risks related to the procedure and long-term immunosuppression. Another approach, involving replacement of the missing enzyme, shows promise in recent studies. But enzyme replacement also has potential limitations, such as the triggering of an immune response against the synthetic enzyme and difficulties getting the protein into the lysosome where it is needed, explained Bedwell.

Gentamicin has its own potential problems as a treatment for Hurler syndrome, however. Aminoglycosides do not cross the blood-brain barrier very efficiently, so it remains to be seen whether the amounts that do reach the brain are sufficient to prevent mental retardation in patients with the disorder.

Gentamicin's potential nephrotoxicity and ototoxicity are other issues for consideration. However, the UAB researchers found that gentamicin boosted enzyme activity for up to 2 days after treatment, suggesting that it may be possible to give the drug intermittently and reduce the risk of these adverse effects.

Other possibilities include administering gentamicin in combination with agents that have the ability to block the aminoglycoside's adverse effects, or finding a compound that has gentamicin's ability to suppress stop mutations but lacks gentamicin's toxic effects, Bedwell said.

## **CYSTIC FIBROSIS STUDIES**

Gentamicin's therapeutic effect would likely extend to other genetic diseases where the patient's gene defect involves a stop mutation. In cystic fibrosis (CF), for example, roughly 10% of cases are caused by a nonsense mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene.

Pilot studies involving patients with CF caused by this nonsense mutation hint that gentamicin can partially restore *CFTR* protein function. Researchers in Israel found that when patients with CF caused by a stop mutation were given nose drops containing gentamicin, there was improvement in one measure of *CFTR* protein function, a test that detects transport of chloride ions across the nasal epithelium, a sign of restored *CFTR* gene expression (*Am J Respir Crit Care Med.* 2000;161:860-865).

In a study that will be published later this year, UAB researchers administered intravenous gentamicin to 10 patients with CF, half of whom had a nonsense mutation in the *CFTR* gene. After one week of gentamicin treatment, those with the nonsense mutation showed an improvement in transport of chloride ions that was not seen in the other patients, said Clancy, who led the study.

Studies by researchers at the University of Pennsylvania School of Medicine in Philadelphia offer additional support for the feasibility of nonsense mutation suppression involving yet another genetic

disorder, Duchenne muscular dystrophy (*J Clin Invest.* 1999;104:375381). Using mdx mice—an animal model for the disorder, which is caused by a mutation in the gene encoding a protein called dystrophin—the investigators found that aminoglycoside treatment "could restore dystrophin expression and partially restore muscle function," said Bedwell.

## **KNOCK-KNOCK**

Bedwell and collaborators are currently working to develop a "knock-in" mouse—animals engineered to have an *IDUA* gene with a stop mutation corresponding to the most common human stop mutation.

Bedwell is collaborating with PTC Therapeutics, Inc, a company based in South Plainfield, NJ, that is working to find drugs other than aminoglycosides that can suppress stop mutations. The knock-in mouse will help researchers test aminoglycosides—perhaps in combination with other agents that have the ability to reduce adverse effects—and allow them to screen other compounds for ability to suppress stop mutations and boost enzyme levels.

"Down the line, we hope to find something that doesn't have the toxic side effects of the aminoglycosides and does have better permeability across the blood-brain barrier," said Bedwell.

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