New Capreomycin Derivatives for the Treatment of Multidrug-Resistant Tuberculosis

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The Wisconsin Alumni Research Foundation (WARF) is seeking commercial partners interested in developing methods of using the capreomycin gene cluster to develop improved therapeutics for the treatment of tuberculosis.

OVERVIEW

In recent years, multidrug-resistant forms of tuberculosis (MDR-TB) have become widespread. Because MDR-TB does not respond to first-line drugs such as isoniazid or rifampicin, second-line drugs such as capreomycin are increasingly being used. Capreomycins are particularly promising because they are the only drugs that are bactericidal against non-replicating Mycobacterium tuberculosis, the causative agent of tuberculosis. This suggests that they could be used to treat latent tuberculosis infections, in addition to active infections.

However, capreomycin has many undesirable side effects and limited bioavailability. Because no practical mechanism for producing modified capreomycin currently exists, metabolic engineering of the capreomycin pathway to create derivatives with more desirable characteristics has not been feasible. Chemical synthesis of this therapeutic is extremely challenging as it requires 27 steps, and the bacteria that produce capreomycin, Saccharothrix mutabilis subspecies capreolis, are not amenable to genetic manipulation.

THE INVENTION

UW-Madison researchers have isolated and sequenced the capreomycin gene cluster from the bacteria S. mutabilis subspecies capreolus. They transformed the genetically tractable bacteria Streptomyces lividans, which do not naturally produce capreomycin, by using a vector containing this gene cluster. The transformed bacteria were then able to produce capreomycin, making metabolic engineering of capreomycin and capreomycin derivatives possible for the first time.
APPLICATIONS

• Treatment of MDR-TB

KEY BENEFITS

• Provides—for the first time—the production of capreomycin in a foreign host
• Enables the development of improved forms of capreomycin that may have increased bioavailability and renewed activity against MDR-TB
• May result in purer capreomycin with fewer side effects
• May lead to increased patient compliance to the extensive TB treatment course, which in turn should reduce the emergence of further drug resistance

ADDITIONAL INFORMATION

Tech Fields
Drug Discovery - Drug production & design

CONTACT INFORMATION

For current licensing status, please contact John Nagel at jnagel@warf.org or (608) 265-7956.