

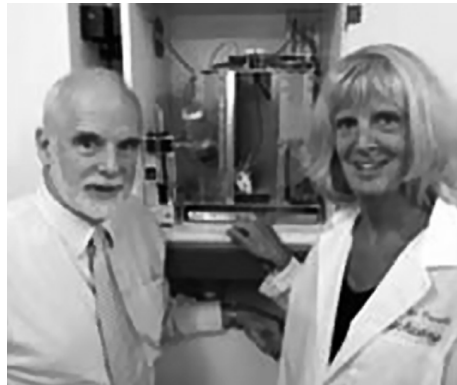
# Cracking Cocaine Addiction: A Gene Therapy Approach

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Cocaine addiction is one of the most serious health problems affecting Americans today. There is a high risk of addiction even after a brief period of casual use, the social and psychological impact from addiction is great, and recovery from addiction is extremely difficult. Stephen Brimijoin, Ph.D. and Marilyn Carroll, Ph.D, believe that addiction rates could be reduced and recovery could be eased by using "cocaine-eating" enzymes to speed the breakdown of the drug in the body. Mayo Clinic researchers have developed powerful cocaine "hydrolases" — enzymes that suppress responses to cocaine by destroying cocaine so quickly it cannot act on the brain or other areas of the body. These enzymes appear well suited for gene transfer, a technique that is being perfected in animals. Once made safe for humans, it can potentially be used to deliver these enzymes, and keep drugs from the reward centers of the brain. Delivering these enzymes via gene therapy should have no adverse effects, in contrast to current techniques to blunt cocaine effects on the brain.

This study examines two key aspects: maintaining drug addiction and relapse after quitting. Using her expertise with behavioral modeling, Dr. Carroll has created a rat model to examine both these phases: Maintaining addiction is studied by requiring addicted rats to press a bar an increasing number of times to receive each self-administered, intravenous cocaine injection. Once addicted, the rat is denied the drug for several weeks, extinguishing the addictive behavior, and then the experimenter



gives a single injection of cocaine to study reinstatement of the lever pressing (relapse). The results will increase understanding of the biology of addiction and test the concept that cocaine abuse might be effectively treated by methods that block drug access to targets in the brain. "Relapse is a critical component of the study since chronically recurring drug abuse is a major challenge to treatment," says Dr. Carroll. "In fact, most individuals who undergo treatment for addiction have a greater than 80% chance of relapse, even after long periods of abstinence."

This project is a perfect illustration of the synergy between Mayo Clinic and the University of Minnesota. Dr. Brimijoin and his colleagues have engineered a therapeutic protein and gene transfer process that could be sustained in a patient and used as a long-term treatment. Key portions of the technology and the final product are unique to Mayo Clinic. Dr. Carroll's nationally-recognized expertise does not exist at Mayo Clinic. They provide the perfect complement to each other and allow research that could otherwise not occur.

## Minnesota Benefits

In addition to cocaine, the enzymes in this study are also important in detoxification

of heroin, so this model could be applied to opiate abuse. Stemming addiction of methamphetamine, a very common and dangerous drug today, is a more challenging goal for gene transfer, but not impossible. Success with cocaine hydrolases serves as a first step in identifying or engineering enzymes effective against methamphetamine and its derivatives.

The Partnership's high-tech attack on drug addiction highlights Minnesota's continuing commitment to solve this growing health problem. Success will enhance the reputation of Mayo Clinic and the University as centers of research excellence on addiction in general, and will help bring additional federal research dollars into the state.

"This project has the potential to impact not just cocaine addiction, but the more global problem of drug addiction," notes Dr. Brimijoin. "The health care costs, psychological devastation and social costs are enormous, which is why developing ways to prevent and treat addiction is so important."

## Promise of Commercialization

This study holds excellent promise for commercialization. Both enzymes in this study are nearing readiness for clinical trials as therapies for drug overdose. The gene transfer technique may be ready within the decade to be tested as an adjunct therapy for cocaine dependence. Other applications are conceivable. For example, the Department of Defense has issued at least one substantial contract for transgenic production of a similar enzyme for protection against terrorist or military use of nerve agents.