For a WEB EXTRA with video coverage of the talks during the public portion of the AIDS conference noted at left, see dartmed.dartmouth.edu/f10/we04.

Drug combo may curb alcohol abuse

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Chau, Green, and Gulick—from the left—hope to start a clinical trial soon.

Seventeen years ago, psychiatrist Alan Green, M.D., noticed something unusual about a group of patients with schizophrenia who were taking a medication called clozapine: not only did their symptoms improve, but they also stopped drinking alcohol. Unfortunately, clozapine has some serious side effects, so it is used mostly as a last resort. Still, since schizophrenia and substance abuse often go hand in hand, and even moderate abuse can worsen schizophrenia, Green was fascinated by the connection.

His primary research goals ever since have been to understand how clozapine works in the brain and to build a clozapine-like drug to treat schizophrenia and substance abuse, but without clozapine's toxic side effects. Recent advances have put both goals in sight.

Model: Green and two researchers in his lab, David Chau, Ph.D., and Danielle Gulick, Ph.D., have taken apart the actions of clozapine by studying its effects on Syrian golden hamsters. These animals make a good model for this research because they will drink alcohol regularly but in moderation, a pattern that mimics the alcohol use of many people with schizophrenia.

Clozapine "may be changing the [reward] circuit," says Green.

So far, the effect of clozapine on the hamsters is consistent with what Green and others have observed in patients: the medication seems to drastically limit alcohol use, without affecting the animals' food intake or other behaviors. "Clozapine's only strong effect [in the hamsters] is on alcohol," says Green, who chairs the Department of Psychiatry.

This finding, published in *Neuropharmacology*, makes clozapine unique. Most medications for addiction take one of three approaches, explains Gulick. Some dampen the drug's effect, but that can lead people to simply use more to get an effect. Others essentially replace the drug being abused with one that has a similar but less detrimental effect, but that can lead to addiction to the substitute. The third approach is medications that make people sick when they abuse their drug of choice. An example of the latter is Antabuse for alcoholism. But, Gulick says, some people just stop taking Antabuse if they intend to drink. Clozapine seems different. It doesn't block the effect of alcohol, make people sick when they drink, or produce any type of high by itself.

Key: Green believes that the key to clozapine's success at reducing patients' use of alcohol lies in how it affects neurotransmitters in the reward circuitry of the brain. This circuitry is a collection of biochemical pathways and structures that regulates behavior by inducing pleasurable sensations. It's what gives people that happy feeling when they think about eating chocolate, having sex, or earning money. In healthy adults, for example, anticipating a monetary reward has been shown to increase levels of dopamine, an important neurotransmitter.

Imaging and animal studies conducted by Green, DMS's Robert Roth, Ph.D., and other scientists have shown that the brains of people with schizophrenia don't respond the same way as the brains of healthy people to such stimuli. So Green believes that people with schizophrenia often drink and use drugs (mainly marijuana or cocaine) because doing so may temporarily correct their dysfunctional brain-reward circuitry—even if, in the long term, it worsens their underlying psychiatric disease.

Circuit: "It could be that clozapine is not blocking the ability of alcohol to have an effect on the circuit, but that it may be changing the circuit," says Green. "We hope that our imaging studies may help us sort that out." Either way, it's clear that clozapine has a dramatic effect on certain neurotransmitters. Years ago, Green found that in patients taking clozapine, levels of one neurotransmitter, norepinephrine, were four times higher than without the drug. Clozapine also increases dopamine levels, but to a lesser degree. The regulation of these neurotransmitters results from clozapine's ability to block certain receptors in the brain, increasing the availability of the chemicals. "But that's not the whole story," says Green. "We think there's another important component." His research group plans to publish a paper soon on findings that may add to the understanding of how clozapine affects the brain.

Toxicity: Chau, Gulick, and Green are getting closer to achieving Green's other primary goal, too. They may have found a way to combine several different medications to get an effect similar to clozapine's, but without its toxicity. They have tested the combination in hamsters and other rodents and submitted an application to the National Institutes of Health to fund a trial in humans.

"This is translational research," Green says with enthusiasm. The term may be overused these days, but it fits in this case. What began as an observation about an interesting side effect—the impact of clozapine on patients' drinking habits—was investigated in the lab and then developed into a potentially important treatment that is now making its way back to patients. JENNIFER DURGIN