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Giving Hope Through Research: A Search for Novel Treatments for Parkinson's Disease, Depression and Drug Abuse

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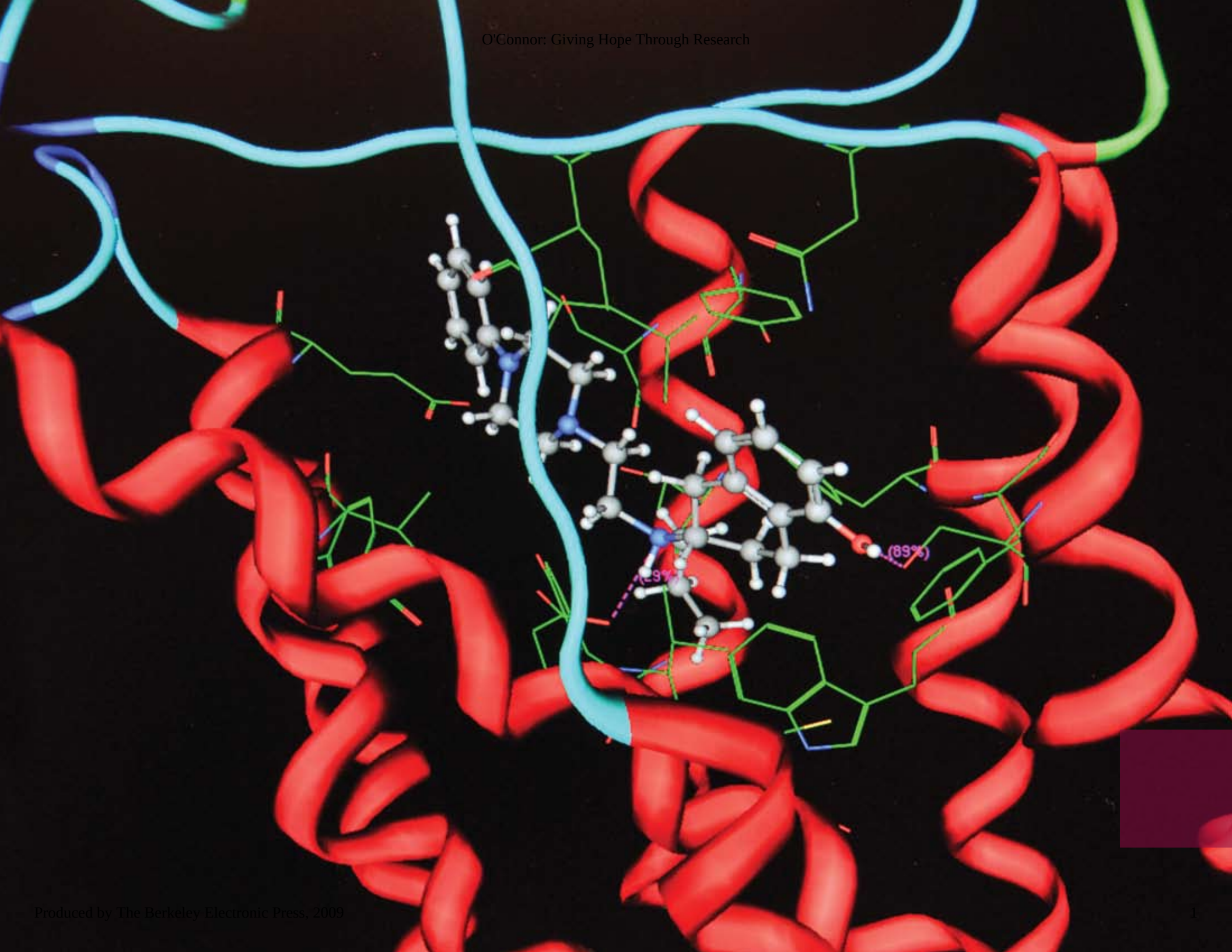
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Giving Hope Through Research

A search for novel treatments for Parkinson's disease, depression and drug abuse

by Julie O'Connor

Parkinson's disease affects approximately one percent of people older than 65 years of age. Nearly one million people in the United States have been diagnosed with Parkinson's disease, a chronic and progressively debilitating disorder. This motor system disorder which causes trembling in hands, arms, legs, jaw and face; stiffness of the limbs and trunk; slowness of movement; and impaired balance and coordination, is the result of the loss of dopamine-producing brain cells.

While there is great hope in Parkinson's disease research, there is no cure. A variety of medications provide relief from the symptoms, including levodopa, also known as L-dopa, that converts into dopamine as it reaches nerve cells in the brain. Levodopa therapy often results in the emergence of motor complications and eventually patients may not respond to the drug. Multiple years of L-dopa

Dr. Aloke Dutta, professor of pharmaceutical sciences and Dr. Prashant Khardar post-doctoral fellow, pharmaceutical sciences

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treatment can cause severe side effects and possible neurotoxicity leading to the withdrawal of use of the drug.

But an answer to why Parkinson's disease develops in some patients and a cure for it remains a mystery. "No ideal therapies are available for slowing the progression of the degeneration process and at the same time relieving symptomatic abnormalities associated with the disease," said Aloke Dutta, Ph.D., professor of pharmaceutical sciences and medicinal chemistry in the Eugene Applebaum College of Pharmacy and Health Sciences at Wayne State University.

Dr. Dutta aims to change this by developing a neuroprotective therapy that may slow down the degeneration process. By developing new drugs that focus on relieving motor dysfunction while at the same time introducing other properties that will reduce oxidative stress in the brain, Dr. Dutta hopes to promote survival of more dopamine neurons and at the same time provide symptomatic relief of the disease.

Still early in their NIH-supported research, Dr. Dutta and his research team have developed some initial lead molecules with multifunctional activities which appear to exhibit some of the desired properties required for neuroprotection effects along with the property to alleviate motor dysfunction. Dr. Dutta and his interdisciplinary research team are collaborating with researchers at New York University School of Medicine and Baylor College of Medicine. Together they are combining drug discovery and computational chemistry along with in vitro and in vivo pharmacology, which ultimately will intensify development of such agents in the near future.

Promising new antidepressant technology

Dr. Dutta is also addressing drawbacks in current antidepressant treatments. Major depression is a disorder posing significant health problems. After cardiovascular disease, depression is considered the second most debilitating disease in the world. "Drug therapies currently on the market for treatment of depression have many problems and shortcomings," said Dr. Dutta. "A number of the therapies don't work for a significant number of patients, and some treatments work at first, but later are ineffective."

According to Dr. Dutta, these treatments don't address the dopamine component needed to interact with the relevant targets in the brain. Dr. Dutta and his research team along with collaborators from the New York University School of Medicine have discovered that by combining three monoamine transporters blocking activities into a single molecule, a new generation of antidepressants could be developed. One such lead polyfunctional molecule discovered in Dr. Dutta's laboratory interacts with norepinephrine, serotonin and dopamine systems in the brain, and exhibited remarkable activity in preclinical in vivo antidepressant tests, indicating that it might possess a potent antidepressant activity.

> "We believe a suitable treatment for such a devastating addiction will not only help people with overcoming such addictions, but also reduce a heavy economic burden of our society."
>
> **— Dr. Aloke Dutta**

"One of our goals will be to study whether such novel triple uptake inhibitor molecules can produce more desirable therapeutic profiles as antidepressant agents compared to the current existing drugs and whether their chronic exposure might lead to the production of neurotrophic factors in the central nervous system via gene expression," said Dr. Dutta. "This study has the potential to lead to other possible applications, such as treatment of obesity and neuropathic pain. This patent pending technology has great promise to make a difference in the lives of many," he added.

Finding a treatment for cocaine dependency

According to the 2003 National Survey of Drug Use and Health, over 2.1 million U.S. adults reported using cocaine within 30 days prior to the survey. Currently no medication is approved for clinics to treat this addiction.

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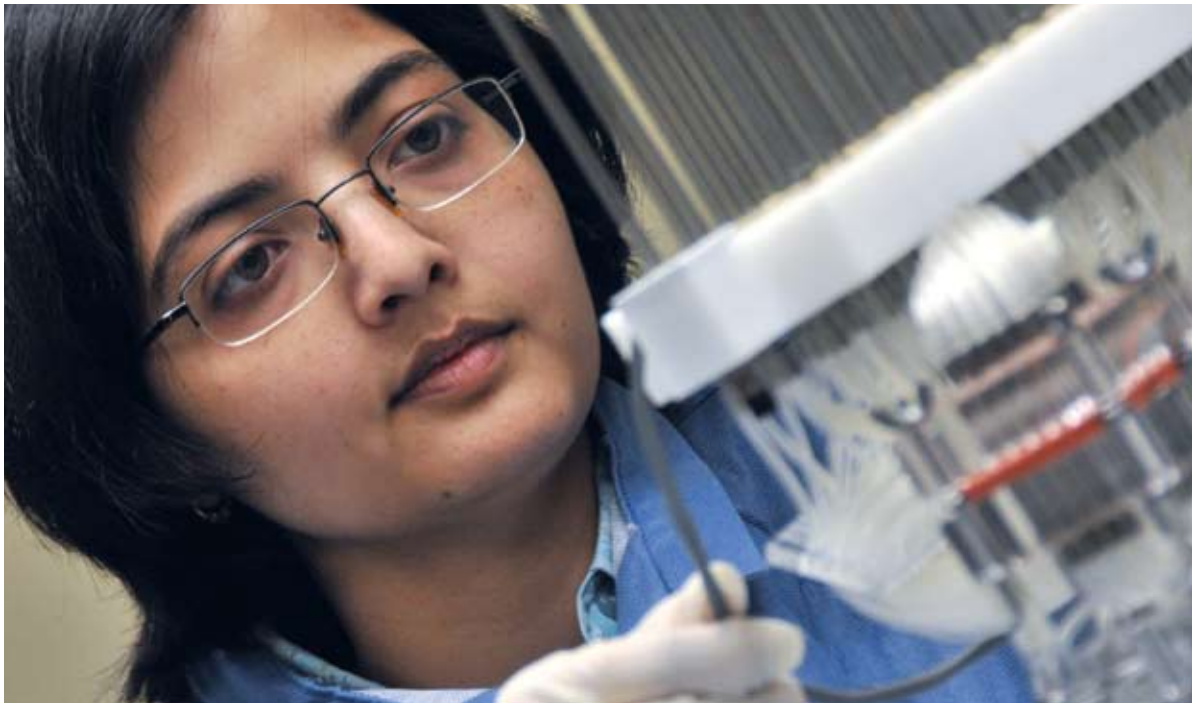
"The evidence from preclinical studies suggests that the reinforcing effect of cocaine that promotes its abuse is mostly mediated by blockade of the presynaptic dopamine transporter resulting in modulation of dopaminergic activity in the mesolimbic or meso-accumbens dopamine reward system of the brain," said Dr. Dutta. With repeated use, cocaine can cause long-term changes in the brain, leading to addiction. Tolerance to the cocaine high often develops, causing users to increase the amount they use to intensify and prolong the euphoria, which often leads to an increased risk of adverse psychological or physiological effects.

Dr. Dutta's research in the field of drug abuse has been supported by NIH for a number of years. "Our effort to combat cocaine addiction is directed toward rational development of small molecules targeting the sites of interaction of cocaine in the brain that are responsible for its strong reinforcing effect," said Dr. Dutta. Dr. Dutta's research team, which includes collaborators from New York University School of Medicine and Virginia Commonwealth University, employs in vitro and in vivo behavioral pharmacology and molecular biology studies to understand the potential of new drugs as treatment agents. His team recently identified a promising lead compound, D-84, which interacts specifically with the dopamine transporter. Currently, this compound is undergoing extensive preclinical in vivo evaluation to explore its potential to treat cocaine and methamphetamine abuse. Several other molecules are also being investigated.



"We believe a suitable treatment for such a devastating addiction will not only help people with overcoming such addictions, but also reduce a heavy economic burden of our society," commented Dr. Dutta.

About Dr. Aloke Dutta: Dr. Dutta received his B.S. in Chemistry and M.S. in Organic Chemistry from Calcutta University, Calcutta, India and his Ph.D. in Organic Chemistry from Ohio University. He joined Wayne State University in 1998.