Nanomedicine for Drug Addiction

WORKING TO SILENCE A GENE THAT TRIGGERS ADDICTIVE BEHAVIORS

A potentially new nanotechnology treatment for drug addiction was described by UB clinical and basic scientists in a paper published online in the *Proceedings of the National Academy of Sciences (PNAS)* the week of March 23.

Their work describes a stable nanoparticle that can deliver specialized ribonucleic acid (RNA) molecules, known as short-interfering RNA, or siRNA, in the brain to "silence" or turn off a gene that plays a critical role in many kinds of drug addiction.

By Ellen Goldbaum

PHOTO BY DOUGLAS LEVERE

The UB researchers working on a new nanotechnology treatment for drug addiction are, clockwise from front left, Hong Ding, PhD; Indrajit Roy, PhD; Rajiv Kumar, PhD; Earl J. Bergey, PhD; Ken-Tye-Yong, PhD; Adela C. Boniou, PhD; Stanley A. Schwartz, MD, PhD; Supriya D. Mahajan, PhD; Paras N. Prasad, PhD; and Rui Hu. All are active participants in the strategic strength in Integrated Nanostructured Systems identified in the UB 2020 planning process, which brings together researchers in the life sciences, medicine and engineering to promote interdisciplinary advancements.

"THESE FINDINGS mean that in the future we might be able to add a powerful pharmaceutical agent to the current arsenal of weapons in order to more effectively fight a whole range of substance addictions," says Paras N. Prasad, PhD, executive director of the UB Institute for Lasers, Photonics and Biophotonics and SUNY Distinguished Professor in the Department of Chemistry, who led the UB team.

The new approach developed by the UB researchers also may be applicable to treating Parkinson's disease, brain cancer and a range of other neurologic and psychiatric disorders, which require certain drugs to be delivered to the brain.

At the same time, the study's coauthors in the UB Department of Medicine say this highly translational research strongly suggests that the nanoparticles would be applicable to other diseases. They will soon begin to study their use in treating AIDS dementia, prostate cancer and asthma. "The findings of this study tell us that these nanoparticles are both a safe and very efficient way of delivering highly sophisticated new drugs that turn off abnormal genes to a variety of tissues," says Stanley A. Schwartz, MD, PhD, director of the Division of Allergy, Immunology and Rheumatology in the UB Department of Medicine, who is a coauthor on the study.

Schwartz says that the study's success underscores how collaborations among researchers in the physical and clinical sciences can lead to valuable translational findings.

"This study shows how you can take very solid and important, high-tech findings in the physical sciences—for example, chemistry—and utilize those technologies for the eventual treatment of patients," he observes.

Researchers at the Institute for Lasers, Photonics and Biophotonics have spent years developing specialized nanotechnologies as highly customized delivery vehicles for pharmaceuticals, while the researchers in the Division of Allergy, Immunology and Rheumatology have developed an expertise in specific aspects of HIV-AIDS, drug addiction and complications that can occur in AIDS patients who also are drug abusers. They also have validated a blood-brain barrier model that played an important role in the research described in *PNAS.*

The *PNAS* paper describes the development of an innovative way to silence DARPP-32, a brain protein understood to be a central "trigger" for the cascade of signals that occurs in drug addiction.

Silencing of the DARPP-32 gene with siRNA can inhibit production of this protein and thus could help prevent drug addiction.

"When you silence this gene, the physical craving for the drug should be reduced," says Adela C. Boniou, PhD, a postdoctoral researcher at the Institute for Lasers, Photonics and Biophotonics in the UB Department of Chemistry in the UB College of Arts and Sciences, and a coauthor.

The drawback has been in finding a way to safely and efficiently deliver the siRNA, which is not stable by itself.

The UB researchers were successful when they combined the siRNA molecules with gold nanoparticles shaped like rods, called nanorods.

This may be the first time that silencing RNA molecules have been used with gold nanorods.

"What is unique here is that we have applied nanotechnology to therapeutic concepts directed at silencing a gene in the brain using RNA techniques," says Supriya D. Mahajan, PhD, research assistant professor in the Department of Medicine in the School of Medicine and Biomedical Sciences, and coauthor.

In addition to their biocompatibility, the gold nanorods developed by the UB researchers are advantageous because they are rod-shaped rather than spherical, thus allowing for more siRNA molecules to be loaded onto their surface. This further increases their stability and allows for better penetration into cells.

"We have demonstrated that we can use these gold nanorods to stabilize the SiRNA molecules, deliver them across the blood-brain barrier and silence the target gene," says Indrajit Roy, PhD, deputy director for biophotonics at the institute. "The nanorods nicely address all three of these requirements."

The nanorods delivered 40 percent of the silencing RNA molecules across the blood-brain barrier model, significantly higher than the amounts that have previously been achieved in other experiments.

In the next stage of the research, the UB scientists will conduct similar experiments in vivo; both groups say they are pleased with the collaboration and that they expect the partnership to to flourish.

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For example, in their studies of AIDS patients, the researchers in the School of Medicine and Biomedical Sciences have been particularly interested in the phenomena of AIDS dementia, where the disease crosses the blood-brain barrier.

"IN THE *PNAS* PAPER, much of what we are suggesting could work for addictive behaviors can be directly translated to some of the more severe aspects of AIDS dementia," says Schwartz.

He adds that AIDS dementia is usually irreversible and fatal but that the collaboration with Prasad's group has given them a promising new avenue to study.

"We think that by using this nanoparticle technology, we might be able to bring antiviral drugs into the brain," he explains.

In addition, Schwartz reports that his group is looking at a range of other diseases that could be similarly targeted. "In fact, the brain is one of the hardest organs to target," he says. "Now that we know it is possible to do that, it opens the possibility that we can consider doing this for a whole range of tissues. Currently we are planning to look at targeting prostate cancer and asthma."

Prasad notes that the team also is studying how to combine other kinds of silencing RNA technologies with nanoparticles to potentially turn off the genes involved in a range of diseases and addictive behaviors, including gambling and obesity.

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"It may be possible to target the biomarkers of specific addictions or compulsive behaviors with similar technologies," he explains.

"This research has reinforced our sense of how valuable are our interactions with basic physical scientists like Dr. Prasad and his group," says Schwartz.

"The partnership between the Institute and the Department of Medicine is the basis of translational medicine," Mahajan concurs. "The biologists are talking to the chemists and vice versa and we are all understanding each other."

The researchers are active participants in the strategic strength in Integrated Nanostructured Systems identified in the UB 2020 planning process, which brings together researchers in the life sciences, medicine and engineering to promote interdisciplinary advancements.

Additional coauthors on the paper are Earl J. Bergey, PhD, research associate professor in chemistry; Rui Hu, senior research support specialist and Hong Ding, PhD, Ken-Tye Yong, PhD, Rajiv Kumar, PhD, all postdoctoral associates in the Institute for Lasers, Photonics and Biophotonics.

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gets some throat injury is very, very small for him personally, it may not be worth it just for the headaches he'll get from opponents, because they do get chirped at."

Another potential objection to neck guards is that they might deflect skate blades to other vulnerable regions of the head and neck area and cause even more serious injuries, but again, there is no good evidence yet.

EMERGENCY RESPONSE GUIDELINES

After the Zednik incident, Bisson participated in efforts to develop a set of emergency preparedness guidelines that were recently adopted by the NHL.

Each year, members of the Team Physicians Society convene in the city where the NHL All-Star Game is held to conduct a hockey trauma course for all the team doctors. "I gave a talk on vascular injuries at our team physicians' meeting in January of this year because I've become sort of an expert on it now, if there is such a thing as a major-vascular-injury-in-an-NHL-rink expert. I've dealt with one of them so I've seen as many as anybody. They wanted to know what worked and what we are going to do to improve things next time."

The Team Physicians Society sets standard protocols for all teams to follow in the event of various emergencies, based on the collective experiences and expertise of its members. Then the teams customize the standards to the unique circumstances of their own arenas. In one city, an ambulance that had to cross railroad tracks was stuck waiting for a train to pass, calling for the development of an alternate route to the nearest hospital.

"We have a team meeting at the beginning of every season," says Bisson. "I call together our training staff and the other medical doctors and our security personnel and the ambulance drivers and everybody else, and we work through the scenarios that could possibly happen, the ones that could be life-threatening. A guy gets hit in the chest and his heart stops. What would you do? He gets hit in the throat. What do you do? A major airway, a major laceration, eye injuries, you can imagine all sorts of crazy things, so we try to focus on the ones that would be most likely among those extremely rare injuries to occur and we say, 'Let's figure out if there's any little barriers that could interfere with us getting treatment for this person,' and we've established protocols that way, as have all the teams in the NHL."

The key to effective emergency response, Bisson says, is anticipation. When you know what to expect and everyone knows in advance what they are supposed to do, you get the kind of results that save lives.

NOT ALL FUN AND GAMES

While it might seem fun to have access to all the rink-side and sideline excitement surrounding two professional sports teams, hobnobbing with the elite players of the NHL and the NFL, consider that the official team physician is in effect the official team worrier. It's evident that Bisson's concern for his players' welfare extends on and off the playing field.

"I'm watching the game differently than you are," he says. "I'm stressing out. I don't want anybody to get hurt. I'm ready to have to run onto the field at any second and deal with somebody who's paralyzed. I watch the play, and then I really watch the end of the play, and I'm looking at this tangle of bodies to make sure that I see everybody stand up. We're watching a different game."

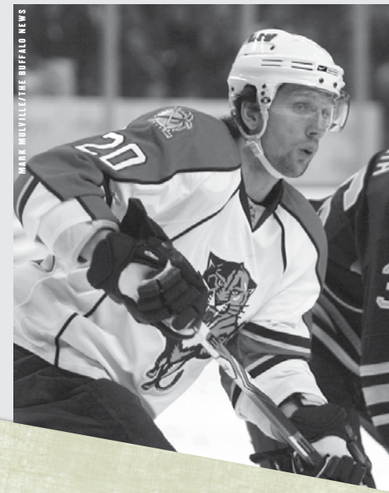
Bisson reports that the neck laceration research project is about three-quarters of the way complete. A case report on Zednik's injury coauthored with McCormack, the attending emergency room physician at BGH, and Noor, Zednik's surgeon, is pending publication in the *American Journal of Sports Medicine.*

"If there were compelling data that came out of this study," Bisson says, "plus some other studies that indicate it's really obvious people should be wearing a neck guard, that's how the decision should be made. I don't expect this one study to answer that question. I think it's a first step toward deciding how much we should worry about neck lacerations happening. Is it incredibly rare? Was Richard Zednik's injury the equivalent of being hit by lightning? I don't know if we'd have to make everybody wear neck guards for that. On the other hand, maybe it's happening more often than we think and we're just lucky that it hasn't been deep enough to kill somebody."

Although Zednik missed the rest of the 2007–08 season, he had a great year with the Panthers in 2008–09. Like the rest of the players in the league, he hasn't been wearing a neck guard. BP

Patrick Klinck is a freelance writer based in Buffalo. He was at HSBC Arena the night Richard Zednik was injured.

Zednik



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