Bound to Survive

Antibody extends life of mice with breast cancer

By Lois Baker

A monoclonal antibody developed by researchers in the School of Medicine and Biomedical Sciences has been shown to significantly extend the survival of mice with human breast-cancer tumors and to inhibit metastasis to the lungs by more than 50 percent.

The antibody, named JAA-F11, targets a particular disaccharide, an antigen known as TF-Ag, which aids the adhesion and spread of certain cancer cells. In the study—results of which were published in the November 2006 issue of *Neoplasia*—researchers showed that while the antibody did not kill the cancer cells, it blocked stages of cancer-cell growth that allow the cells to adhere to organ tissue.

Mice with breast-cancer tumors that received the antibody had a median survival time of 72 days, compared to 57 days for the animals that did not receive JAA-F11, the study found. In addition, exposing cultures of tumor cells to the antibody inhibited cell growth by a statistically significant 16 percent.

"This antibody binds with a carbohydrate on the tumor cell surface that is involved in adhesion of the cell during the metastatic process," explains Kate Rittenhouse-Olson, PhD, associate professor of clinical and laboratory sciences at UB and senior author on the study. "Not only would drugs attached to the antibody JAA-F11 bind to the tumor cell surface to direct their cytotoxic effect, but the binding of the antibody itself would block the cell from metastasizing."

The antibody was tested using in vitro models of tumor cell growth, in assays to determine its ability to damage or kill cells (cytotoxicity), in various models of cancer metastasis, and in mice with metastatic breast cancer.

"In addition to providing a survival advantage," says Rittenhouse-Olson, "JAA-F11 immunotherapy reduced the metastatic tumor burden significantly, reflected by both a dramatic decline in the overall incidence of spontaneous metastasis to the lung—88 percent to 47 percent—and fewer macroscopic metastatic lesions."

The research group currently is determining if JAA-F11 could increase the effectiveness of existing cancer drugs, she says, as well as studying the possibility of using the antibody as a vehicle for the targeted delivery of drugs to aid cancer diagnosis and therapy.

Jamie Heimburg and Jun Yan, co-first authors on the paper, were graduate students in Rittenhouse-Olson's lab at the time of the study.

Also contributing to the research were Susan Morey and Robert Klick, PhD, from the UB Department of Biotechnical and Clinical Laboratory Sciences; Linda Wild, MD '76, from UB's Pathology Department; Olga V. Glinskii, MD, Vladislav V. Glinsky, MD, and Virginia H. Huxley, PhD, from the University of Missouri, and Rene Roy, PhD, from the University of Quebec in Montreal. Glinsky also is affiliated with the Harry S. Truman Memorial Veterans Hospital in Columbia, Missouri.

The research was supported by grants from the National Institutes of Health to Rittenhouse-Olson, Glinskii and Huxley; from the Veterans Afffairs Merit Review Program to Glinsky, and from the U.S. Department of Defense to Heimberg and Rittenhouse-Olson. BP

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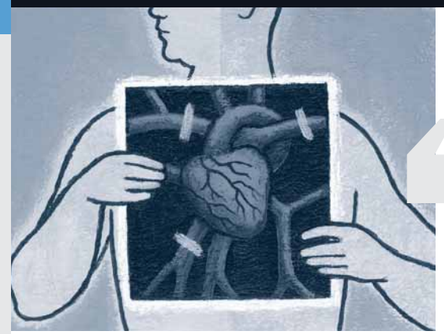
A blood component called glycated LDL—a form of low-density lipoprotein (the "bad" cholesterol) with a sugar molecule attached—is known to be higher in diabetics than non-diabetics, and extensive research has shown that diabetics are at increased risk of a heart attack.

A Link to Explore

"Bad" cholesterol associated with heart-attack risk

By Lois Baker



Now, for the first time, a new study that followed a cohort of elderly people in southern Italy found that glycated LDL levels increase the risk of heart attack in both diabetics and persons without diabetes.

Results of the study, which appeared in the January 2007 issue of *Nutrition, Metabolism and Cardiovascular Diseases,* show that diabetics with the highest levels of the LDL at the start of the study had nearly three times the risk of developing a heart attack within five years than persons with low levels of the LDL. Even in persons without diabetes, those with high glycated LDL levels had twice the risk of having a heart attack.

"The association of glycated LDL with myocardial infarction could explain why diabetes is a risk factor for MI (heart attack)," says Maurizio Trevisan, MD, dean of the UB School of Public Health and Health Professions and senior author on the study.

> These findings need to be confirmed, and if the relationship is confirmed, interventions aimed at lowering the glycation of lipoproteins should be organized to test whether such interventions can lower the risk of coronary heart disease.

"In fact, glycated LDL is more easily oxidized than normal LDL and more easily metabolized by macrophages, the precursors of foam cells of the atherosclerotic plaque," adds Trevisan, a professor of social and preventive medicine. "This is probably because the sugar molecule attached to the apoprotein B of LDL interferes with the link of the apoprotein with its membrane receptor.

"Glycated apoprotein B, like glycated hemoglobin (HbA1c), is present also in non-diabetics and its increase could be due to temporary hyperglycemia, caused by a high-glycemic-load meal, by stress and by other conditions."

The glycated LDL/heart attack study, funded by the Italian Ministry of Health, was an arm of the Onconut Study, an ongoing investigation of lifestyle and dietary predictors of cancer being conducted in persons over 50 years of age in the Apulia region of Italy.

Of 4,452 participants who had not had a heart attack when the study began, 103 people developed a heart attack within five years; 34 of those were diabetics at the start and 69 were not.

All participants had blood samples taken when they entered the study. Levels of fasting glucose, insulin, cholesterol, triglycerides, HDL (the "good" cholesterol), LDL and glycated LDL were measured. When levels of these blood components in those who had had heart attacks (cases) and those who had not (controls) were measured, the only component that was significantly higher in both diabetic and non-diabetic cases was glycated LDL.

Trevisan notes that while the findings provide interesting information, they cannot be applied to the population at large because the study subjects were selected from persons who had sought the services of clinical laboratories affiliated with Italy's National Health Service, not from the general population.

"These findings need to be confirmed," he says, "and if the relationship is confirmed, interventions aimed at lowering the glycation of lipoproteins should be organized to test whether such interventions can lower the risk of coronary heart disease."

The 20-year follow-up of participants in the study, which began in 1992, should provide more concrete data, he adds.

First author on the study was Giovanni Misciagna, MD, PhD, a former doctoral student in epidemiology at UB, now at the Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) in Castellana-Bari, Italy. Additional contributors were Giancarlo Logroscino, from Harvard University's School of Public Health, and Gianpiero De Michele, Vito Guerra, Annamaria Cisternino and Maria Gabriella Caruso, all from the IRCCS. BP

Rewriting Bad Code

Targeting RNA that causes triplet-repeat disorders

A University at Buffalo medicinal chemist has identified compounds to target a ribonucleic acid (RNA) that causes a form of muscular dystrophy called myotonic dystrophy, or DM.

By Ellen Goldbaum

Myotonic dystrophy, a form of muscular dystrophy, belongs to a class of diseases called triplet-repeat disorders in which the genetic code has an abnormal repetition of three letters of DNA.

As with all forms of muscular dystrophy, no treatment currently exists for DM, which is characterized by the inability of muscles to relax at will. Cases of the disease can vary widely in severity based on the severity of the RNA defect and it frequently is diagnosed in the adult years.

According to Matthew Disney, PhD, whose research focuses on developing a chemical code for targeting RNA with small molecules, DM belongs to a class of diseases called triplet-repeat disorders in which the genetic code has an abnormal repetition of three letters of DNA.

"The DNA with the abnormal triplet repeats is made into a defective RNA that forms an unnatural structure that binds to a protein important in muscle function," explains Disney, assistant professor in the Department of Chemistry in the UB College of Arts and Sciences. "It is this RNA-protein interaction that causes the disease."

Disney in 2006 was one of just seven scientists in New York State to be awarded a $200,000 James D. Watson Investigator grant from the New York State Office of Science, Technology and Academic Research. He is using the award for work to target some of these RNA structures with small molecules developed in his lab at UB.

RNA, DNA's chemical cousin, is a template for protein synthesis, which orchestrates protein-building, catalyzes chemical reactions and performs many other essential roles in cells.

Mutations in RNA can alter expression of proteins that can lead to cancer, sickle cell anemia and other diseases, one of which is DM.

Initial research efforts will be focused on validating Disney's approach for designing compounds to target RNA structures, as well as confirming that the DM RNA target is a viable one for treating this disease.

If the early research is successful, then Disney and his colleagues will tackle the much more challenging issue of developing their compound into a viable pharmaceutical treatment.

In addition to the NYSTAR award and funding from the Camille & Henry Dreyfus Foundation, Disney is supported by, and is a member of, UB's New York State Center of Excellence in Bioinformatics and Life Sciences.

A UB faculty member since 2005, Disney graduated from the University of Maryland and earned a master's in chemistry and a doctorate in biophysical chemistry from the University of Rochester. BP

Depth and Breath

Training breathing muscles improves swimmers' performances

By Lois Baker

Swimmers and scuba divers can improve their swimming endurance and breathing capacity through targeted training of the respiratory muscles, researchers at the University at Buffalo have shown.

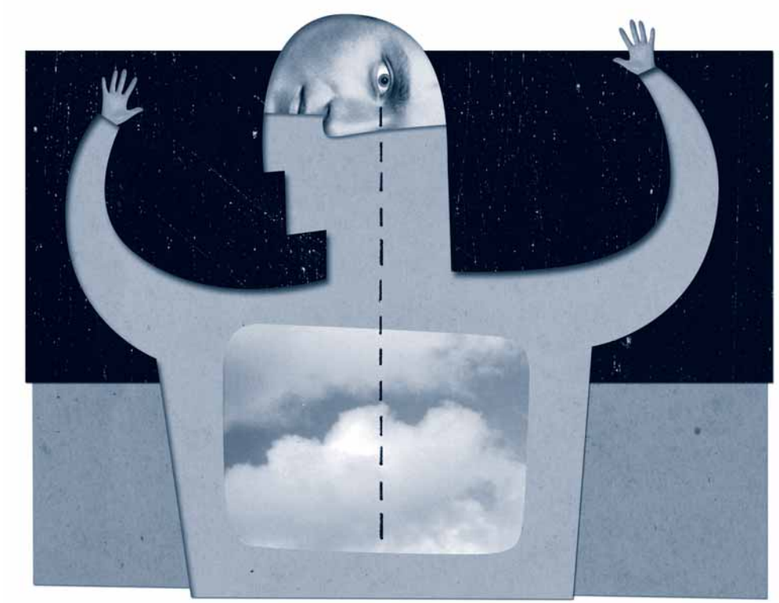
In this pioneering work, subjects who followed a resistance-breathing training protocol (breathing load) improved their respiratory muscle strength and their snorkel swimming time by 33 percent and underwater scuba swimming time by 66 percent, compared to their baseline values. Participants randomized to a similar protocol requiring high respiratory flow rates (endurance) improved their respiratory endurance and surface and underwater swimming times by 38 percent and 26 percent, respectively.

The group randomized to a placebo training program, conducted with the same equipment and protocol, showed no significant improvement in respiratory or swimming performance.

Results of the study, conducted in UB's Center for Research and Education in Special Environments (CRESE), appeared in the February 2007 issue of the *European Journal of Applied Physiology.*

"Specific respiratory muscle training could allow divers in the military, civilian rescue services, commercial enterprises and sport to perform better underwater," explains Claes E.G. Lundgren, MD, PhD, professor of physiology and biophysics in the School of Medicine and Biomedical Sciences and the study's senior author.

David R. Pendergast, EdD, professor of physiology and biophysics, adjunct professor of mechanical and aerospace engineering and CRESE director, along with his research group, were instrumental in the research.



Lundgren says that training the breathing muscles to improve the performance of swimming muscles seems counterintuitive, but is logical physiologically.

"Typically, we think it's the muscles that move the body that are fatigued when we tire," he notes. "However, the increased work load of the breathing muscles is very important, particularly underwater during prolonged or high-intensity exercise such as swimming.

"As shown by other studies, when breathing muscles become fatigued, the body switches to survival mode and 'steals' blood flow and oxygen away from the locomotor muscles and redirects it to the respiratory muscles to enable the diver to continue breathing. Deprived of oxygen and fuel, the locomotor muscles become fatigued.

"Increasing the strength and endurance of the respiratory muscles prevents their fatigue during sustained exercise, enabling divers and swimmers to sustain their effort longer without tiring."

The type of training, adds Lundgren, also may be useful for patients who suffer from respiratory stress.

Juli A. Wylegala, PhD, UB clinical assistant professor of rehabilitation sciences, is first author of the paper. Pendergast, Luc E. Gosselin, PhD, associate professor of exercise and nutrition sciences, and Dan E. Warkander, PhD, research assistant professor of physiology and biophysics, are additional authors.

The research was supported by a grant from the Naval Sea Coastal Systems (Navy Experimental Diving Unit). BP

To learn more about this study and its methodology, visit the UB NewsCenter at www.buffalo.edu/news/ and search "swimmers."

Dentistry without Dread

Researchers study no-drilling, no-shots dentistry

By Lois Baker

Imagine having a decayed tooth repaired, painlessly, without drilling or shots of anesthesia to numb the area.

Wishful thinking? Not if two studies being conducted at UB's School of Dental Medicine show positive results.

In one study, funded by a $100,000 grant by Apollonia, LLC, researchers in the school's Center for Dental Studies are testing a nasal spray that numbs the upper teeth.

"If this study is successful, it may mean the end of dental injections when dentists are performing procedures on the upper arch," says Sebastian Ciancio, DDS, principal investigator on the study.

The study is testing the effectiveness in dental procedures of a topical anesthetic normally used by ear, nose and throat physicians when they operate on the nose. Patients who received this anesthetic for that purpose reported it also numbed their upper teeth, sparking interest in using it for dental procedures.

"We currently are testing to determine what the optimal dose is for this spray when used as an anesthetic agent for the maxillary (upper) teeth," Ciancio explains. "The current study includes 85 patients and should be completed by the end of January; it then will be followed by a second study in March. Once we know the results, we'll then test it in a broader population."

Coinvestigators, all from the UB dental school, are Eugene Pantera, DDS, Sandra Shostad, DDS, and Joseph Bonavilla, DDS.

The second study, set to begin this spring, will test the use of ozone to kill bacteria in a decayed tooth and its potential to eliminate the need for the dreaded drill, at least to repair simple cavities. Researchers at UB and two other U.S. dental schools will conduct the research, which is funded by a $1.5 million grant from Curozone, Inc. and Kavo Dental Manufacturing Company (UB's portion is $400,000).

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Ciancio, who also is the UB principal investigator on this study, says the ozone-delivery device currently is being used in Europe. "If the U.S. studies are successful, it should be available in this country in about two years," he says.

The study will evaluate the effectiveness of the ozone delivery device, which fits over a tooth and forms an airtight seal, in arresting tooth decay. The study will enroll 125 participants and will last 18 months.

"Following application of the ozone, patients will use a remineralizing solution, which strengthens the weakened tooth structure and, in many cases, eliminates the need for any dental drilling," says Ciancio.

Additional investigators on this study are Othman Shibly, DDS, Jude Fabiano, DDS, Benita Sobieroj, DDS, Maureen Donley, DDS, and Nina Kim, DDS, all from the UB dental school faculty. BP