A DMS team analyzed 200 randomly chosen press releases put out by 20 academic medical centers and concluded that they often overstate research findings and fail to acknowledge study limitations.

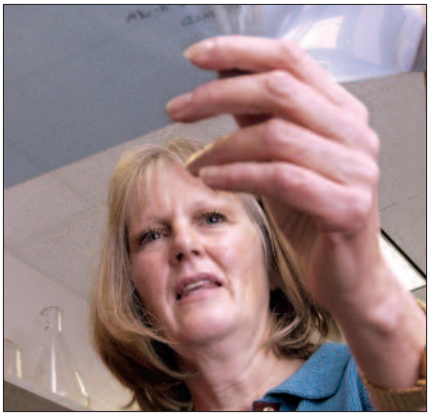
Protein shows promise in reversing plaque

If only "atherosclerosis" weren't such a tongue-twister. The disease kills more Americans than cancer but has nowhere near the frightening ring for most people as the word "cancer." Atherosclerosis involves a buildup within the arteries of fatty deposits called plaque. The arterial wall compensates for the blockage in the blood flow by expanding around the plaque deposits. As a result, atherosclerosis is a "silent" disease until the deposits overwhelm this compensatory mechanism.

A heart attack or stroke caused by a blockage may be the first sign of the disease. By then, irreversible damage has often occurred. Treatment options include lifestyle changes (such as diet, exercise, and smoking cessation), medication, and surgery. There may one day be another option on that list.

The protein reduced cholesterol in plaque deposits by 49%.

Fat: In a paper published in *Circulation Research*, DMS's Mary Jo Mulligan-Kehoe, Ph.D., and colleagues revealed a possible new way to reduce plaque. The team administered a protein molecule called rPAI-1_{23} to mice that had been fed a high-fat diet to foster the creation of plaque deposits. The protein inhibited angiogenesis —the growth of new blood vessels—in the plaque-filled arteries, affecting the plaque's growth and stability. Of particular note was the fact that the protein also reduced the cholesterol in plaque deposits by an impressive 49%. The authors hailed this as "a dramatic effect."



JON GILBERT FOX

Mulligan-Kehoe studied plaque deposits in mice.

Protein: Mulligan-Kehoe explains that rPAI-1_{23} is a truncated form of a parent protein called PAI-1, whose role in angiogenesis remains controversial. "In everything you read about atherosclerosis relative to PAI-1," she says, "they cannot put a handle on whether it's pro- or anti-angiogenic"—that is, whether it promotes or inhibits the formation of blood vessels. And, she adds, "they've looked at it in plaques and they can't tell you whether it's protective or causes plaque progression."

So Mulligan-Kehoe, with funds from two NIH grants plus Philips Imaging, set out to identify the functions of PAI-1. The researchers started by cutting away certain regions of the protein. They found that truncated forms were pro-angiogenic if they contained a certain domain, such as rPAI-Hep_{23}. But when that domain was removed, the truncated protein became anti-angiogenic, such as rPAI-1_{23}.

In addition, using samples of plaque obtained from DHMC patients, Mulligan-Kehoe has shown the presence of both native and truncated PAI-1 in some patients, suggesting that truncated forms of the protein are physiologically relevant.

Lab: The finding that different forms of PAI-1 can be pro- or anti-angiogenic may have application to other diseases as well. Mulligan-Kehoe's lab is also looking at how rPAI-Hep_{23} can improve blood circulation in patients with diabetes.

But as excited as she is about the therapeutic potential of rPAI-1_{23}, Mulligan-Kehoe is eager to continue using it as a tool to study PAI-1. "I just love the science," she says. TINA TING-LAN CHANG

Rural complications

For people with HIV, depression is a serious complication. "HIV-infected patients with depression experience poorer physical and social well-being and greater bodily pain," wrote DMS's Timothy Lahey, M.D., et al. in the journal *BMC Infectious Diseases*. HIV patients with depression are less likely to follow treatment regimens strictly, and they have lower CD4 counts. Lahey found that this problem is worse in rural areas, where people with HIV are more likely to suffer from depression than are those in cities—possibly, he concluded, due to a lack of social support systems.

A smoking gun

It's great when an actor lights up the silver screen, but not so great when one lights up *on* the silver screen. That's because, according to research from Dartmouth's Hood Center for Children and Families, smoking in movies encourages adolescents to become smokers themselves. After tracking the film-watching habits and smoking behaviors of about 2,000 adolescents over seven years, the researchers concluded that about a third of those who took up smoking wouldn't have done so if not for repeated exposure to smoking in movies. "The implications of this finding are highly significant for prevention," they wrote in *Pediatrics*.

DMS's Yinong Young-Xu, Sc.D., coauthored a paper showing that the cost of end-of-life care is much higher for minorities than for whites, due mostly to geographic, demographic, and other differences.

Ironing out a problem for CF patients

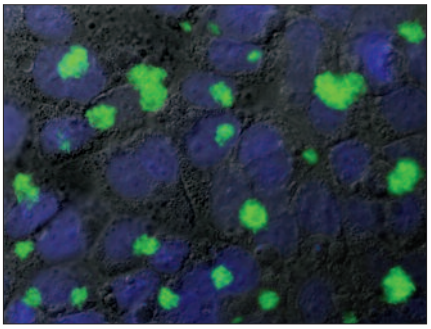
Using chemicals that decrease the availability of iron, a DMS research team has developed a promising new method of attacking the bacteria that infect the lungs of people with cystic fibrosis.

Infection: Cystic fibrosis (CF) is a genetic disease that affects about 30,000 people in the United States. It causes a thick layer of mucus to form in the lungs, providing a welcoming environment for bacteria. The bacterium *Pseudomonas aeruginosa* is particularly problematic, infecting the lungs of about 80% of adults with CF. As the bacterial colonies grow, they cause pulmonary problems and, eventually, premature death. The average life expectancy for people with CF is just 37 years.

The drug combination resulted in a 90% reduction in biomass.

Treatment options are limited. "Once they become infected, there's just no way to get rid of *Pseudomonas*," explains Bruce Stanton, Ph.D., a professor of physiology. "You can suppress it with antibiotics, but you can't get rid of it."

Resistant: One reason for the bacterium's persistence is that it tends to congregate in biofilms—communities made up of vast numbers of bacteria—which make the organism more resistant to antibiotics. Iron also plays an important role in facilitating the formation of biofilms. "It's food for the bacteria," Stanton says.



The green spots are biofilms on the surface of airway cells, and the blue spots are the cells' nuclei.

In previous research, Stanton and a postdoctoral researcher in his lab, Sophie Moreau-Marquis, Ph.D., found that cells in the airways of CF patients release more iron than those in people without CF, exacerbating the problem. "We know iron is important for bacteria to grow, so we wanted to know what happens if we remove iron," says Moreau-Marquis.

To do that, she and Stanton tried two different iron chelators—chemicals that bind to iron, preventing it from being used. They tested the chelators on human airway cells colonized with *Pseudomonas*. On their own, the chelators inhibited the formation of biofilms but did not protect the cells from being damaged by the bacteria.

Stanton and Moreau-Marquis also treated the cells with a standard antibiotic called tobramycin. It mitigated the cell damage to some extent but did not prevent the growth of the bacteria. In fact, the bacterial biomass was even greater after the tobramycin was added.

Dramatic: Then they tried a tobramycin-chelator combination, which helped dramatically. It not only prevented the formation of biofilms, but, when used to treat established biofilms, it resulted in a 90% reduction in the bacterial biomass. "You really have to hit them with the combination of drugs to get the most effect," Moreau-Marquis says.

Stanton points out that the chelators that were tested in the study have already been approved by the FDA for use in humans. "It's relatively easy to take those two in combination and treat patients," he says. To find out just how well this combination therapy will work in humans, Stanton and Moreau-Marquis are now teaming up with physicians in DHMC's CF clinic to put the therapy to the test in a Phase I clinical trial. Amos Esty

Which breast option is best?

Most physicians consider breast-conserving surgery the better treatment for women with early-stage breast cancer, but many such women opt for a mastectomy. A DMS team led by E. Dale Collins, M.D., surveyed 125 patients before they learned about their options, after they watched an informational video, and after they talked to a surgeon. The researchers concluded that the women understood the options' risks and benefits, but 44 of them still chose mastectomy. Collins wrote in the *Journal of Clinical Oncology* that even "when women fully comprehend the key facts, many will [prefer] mastectomy, the more invasive procedure."

Assessing steroid effects

High-profile male athletes make headlines when they're caught taking steroids, but it's not just men who use performance-enhancing drugs. "Young women constitute the demographic with the most rapidly increasing AAS [anabolic androgenic steroid] use," reported a DMS team in *Neuroscience*. To learn more about the side effects of steroids in women, the researchers administered three types of AASs to female mice and found that the steroids altered signaling in a region of the brain that's involved in aggression and anxiety, possibly hinting at behavioral effects of steroid abuse in women.

DMS grad student Courtney Kozul coauthored a paper showing that even low levels of exposure to arsenic, like those often found in well water, increase susceptibility to the H1N1 flu virus.

Manipulating proteins facilitates division

A team of DMS researchers has found a way to help tumor cells solve a difficult division problem.

Before a cell divides, it creates a copy of its chromosomes. As the cell splits, the paired copies are divvied up between the two daughter cells. In tumor cells, however, both chromosomes often end up in the same daughter cell, leaving the other one with fewer chromosomes.

Role: This tendency—known as chromosome instability—is bad news. It's an indicator of a poor prognosis and an increased likelihood of metastasis. DMS biochemist Duane Compton, Ph.D., explains that chromosome instability complicates treatment by helping tumors evade the effects of chemotherapeutic drugs. But Compton and three researchers in his lab—graduate students Samuel Bakhoum and Sarah Thompson and postdoctoral fellow Amity Manning, Ph.D.—identified two proteins that play an important role in regulating chromosome segregation. By manipulating levels of these proteins, they facilitated correct chromosome division—the first time anyone has successfully suppressed chromosome instability. They reported their findings in *Nature Cell Biology*.

"So . . . these tumor lines that are unstable now become stable."

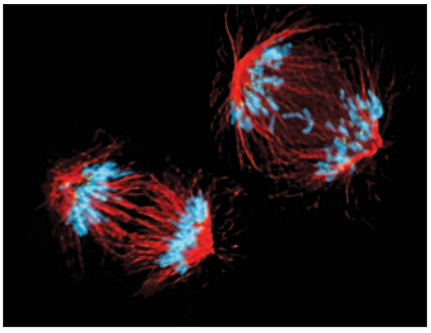
The DMS team examined tumor cells during mitosis. Thin fibers called microtubules extend from opposite sides of the cell and attach to the chromosomes. When all goes well, one chromatid (a copy of the duplicated chromosomes) attaches to fibers on one side, and the other to fibers on the opposite side. Then the fibers pull apart the chromatid pairs and the cell divides, leaving each daughter cell with one copy of each chromosome.

Sometimes, however, fibers from both sides of the cell attach to a single chromatid. It's a common occurrence, Compton says, but usually the incorrect attachments are fixed. His team identified two proteins—Kif2b and MCAK—that allow cell division to proceed correctly. "Their job is to destabilize those attachments," Compton says. "One is acting kind of early in the process of mitosis, and then it gets shut down and the other one acts a little later."

But if those proteins don't do their job, as often happens in tumor cells, a chromatid attached to fibers from both sides may go in the wrong direction. When that occurs, one daughter cell will have more chromosomes than the other.

Stable: Once they identified these proteins, the researchers were able to make tumor cells segregate properly by increasing the amount of Kif2b and MCAK during mitosis. This even suppressed chromosome instability for another 50 generations in tumor cells. "So," says Compton, "we can make these tumor lines that are unstable now become stable."

Eventually, this knowledge could provide new ways of fighting tumors. One possibility is that suppressing chromosome instability may make tumors more responsive to chemotherapy. Or, he adds, it may be possible to hinder tumor growth by *increasing* instability to a point where the cells are no longer viable. Amos Esty



The left cell is dividing properly, but the right one shows a chromosome segregation defect. The chromosomes are blue and the microtubules are red.

Talking to teens

A $100 personal digital assistant (PDA) can improve communication between primary-care physicians and adolescents. For teens, "health risks occur mainly because of behavioral rather than biomedical issues," wrote DMS researchers in *Archives of Pediatrics and Adolescent Medicine*. Using PDAs, they asked teens at five primary-care practices to answer a series of questions about nutrition, exercise, drug use, and other behaviors before their check-ups. Those who did the digital screening were more likely to discuss behavioral health risks with the physician.

Unlocking genetic secrets

Jason Moore, Ph.D., a DMS geneticist, was part of an international team of researchers who reported in the journal *Science* the results of a large-scale study of the genetics of Africans and African-Americans. The researchers analyzed DNA from thousands of people and determined that Africans are descended from 14 ancestral populations. Generally, genetic differences corresponded to cultural and linguistic diversity. The data may eventually be used to help design medical treatments. "Our in-depth characterization of genetic structure in Africa benefits research of biomedical relevance in both African and African diaspora populations," the authors wrote. ■