

In the Lab

Burkholderia Beware

Nanoemulsions target infection deadly to cystic fibrosis patients

EVEN THOUGH IT'S A COMMON BACTERIUM found in soil and water, most people have never heard of *Burkholderia cepacia*. These hardy microbes are usually harmless, unless you have cystic fibrosis or a lung condition called chronic granulomatous disease (CMD). For people with these diseases, *Burkholderia* infection is a death sentence.

"Every CF patient knows about

fibrosis, but with more CF patients living into adulthood, LiPuma says it's a growing problem. About 10 percent of adults over age 18 with cystic fibrosis are infected, he says. Even if they avoid *Burkholderia*, CF patients remain vulnerable to other drug-resistant bacterial killers.

LiPuma has been collecting and studying antibiotic-resistant bacteria since the mid-1980s. He says he's been

Professor of Biologic Nanotechnology, to discuss testing a nanoemulsion called NB-401 against *Burkholderia* and other drug-resistant bacterial pathogens that infect CF patients.

The collaboration between Baker and LiPuma was encouraged by Carroll Haas, president of the Carroll J. Haas Foundation. The foundation, which has supported LiPuma's research for many years, provided funding that allowed the promising new research to begin.

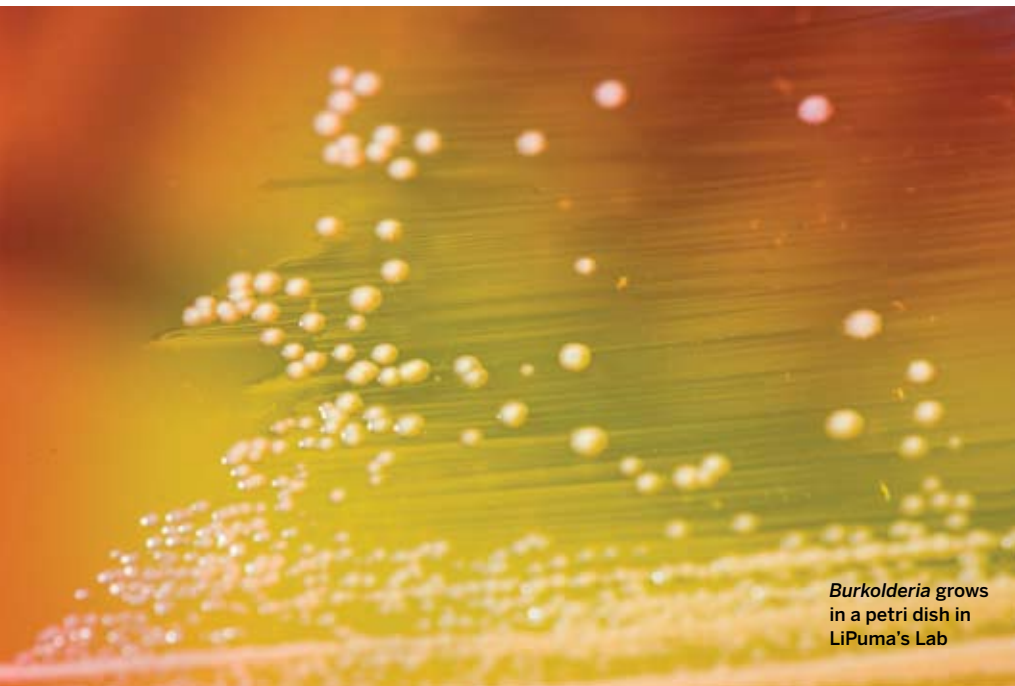
Nanoemulsions are made from ultra-small droplets of soybean oil and agents that affect surface tension suspended in water. Baker developed the technology and founded an Ann Arbor company called NanoBio Corporation to develop and market it.

"Nano-sized particles interact with bacterial cell membranes in ways that disintegrate and kill the cell," explains Joyce Sutcliffe, Ph.D., NanoBio's vice president for research.

LiPuma admits he stacked the deck against NB-401. He searched his repository of 20,000 specimens for the "most drug-resistant bacteria I could find." LiPuma selected 75 strains of *Burkholderia* and 75 strains of other bacteria found in people with cystic fibrosis. He put the bacteria into test tubes with various concentrations of the nanoemulsion and waited to see what happened.

Much to LiPuma's surprise, "It killed everything," he says. "We could dilute it 16-fold and still get very good killing."

To make it more of a challenge, LiPuma then tested NB-401 on bacteria



Burkholderia grows in a petri dish in LiPuma's Lab

Burkholderia and it strikes fear in their hearts," says John LiPuma, M.D., professor of pediatrics and communicable diseases. "It's highly resistant to all antibiotics, and essentially incurable."

Scientists don't know why these bacteria are lethal to people with cystic

contacted many times over the years by people who believe they've found something new to kill *Burkholderia*. Nothing ever has worked.

So it was with some degree of skepticism that LiPuma met with James Baker, M.D., the Ruth Dow Doan

in sputum from CF patients, which can neutralize many antibiotics, and on bacteria growing in biofilms. Biofilms are collections of microorganisms that attach to a solid surface and form a protective envelope around the bacteria inside, making them especially resistant to the effects of antibiotics. While it required stronger concentrations of the nanoemulsion to kill the bacteria, “NB-401 passed every test,” LiPuma says.

Currently, LiPuma is testing NB-401’s bacteria-killing effects in mice infected with *Burkholderia*. He wants to test the nanoemulsion’s bug-killing ability when it’s aerosolized with saline solution and inhaled into the lungs. If drugs for CF infections can be targeted directly to the site of infection, it may be possible to give higher doses without the side effects and complications caused by high doses of antibiotics given systemically.

Based on the encouraging results from LiPuma’s initial tests of NB-401, NanoBio Corporation is convening an advisory panel of cystic fibrosis experts to evaluate the preliminary data and recommend how the company should proceed. Taking a new drug through the pre-clinical and clinical testing required by the U.S. Food and Drug Administration is expensive and risky. It’s a high-stakes decision for any business, especially a small company like NanoBio, but clinical studies are the only way to know if a new treatment will work.

“Potentially, this could be an important advance for the treatment of cystic fibrosis, but we need to test it in people to know for sure,” says Baker.

—SALLY POBOJEWSKI

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HPV Strikes Again

HEAD AND NECK CANCER

used to be most common in older people who drank alcohol, smoked or chewed tobacco. But now physicians are encountering what Thomas Carey, Ph.D., professor of otorhinolaryngology, calls an epidemic of oral head and neck cancers in younger men and women. These tumors of the tonsils and base of the tongue often develop in patients who don’t smoke. They are caused by the sexually transmitted human papillomavirus (HPV) which also causes cervical cancer.



Tom Carey

“Our biggest challenge is determining how best to treat patients with tumors that stem from tobacco and alcohol use, as opposed to tumors linked to HPV,” says Frank Worden, M.D., an assistant professor of internal medicine. “We now know they are two different cancers.”

A one-size-fits-all approach to treating cancer doesn’t work. Every patient’s cancer is unique, and survival depends on choosing the most effective therapy for each cancer. This is especially true for cancer of the mouth, tongue and tonsils. These malignant tumors all look alike, but some are much more dangerous than others.

So how are doctors supposed to know what to do? The answer, according to Carey, Worden and other researchers at the Comprehensive Cancer Center, is in the tumor’s biomarkers. In recent research, these scientists found that patients whose advanced head and neck tumors contained specific molecular markers responded well to chemotherapy and radiation. Patients whose tumors had different biomarkers did not respond to conservative treatment. They required more aggressive chemotherapy, in addition to surgery.

One bit of good news from their research, according to Carey, is that HPV-positive tumors usually responded to conservative chemotherapy and radiation. Patients whose tumors contained high levels of the epidermal growth factor receptor called EGFR in combination with other markers were much less likely to survive even after surgery and aggressive treatment.

Says Carey, “The high incidence of HPV-associated cancers also suggests that all adolescents, not just young women, should be vaccinated against this cancer-causing virus.” —SP [MORE ON THE WEB](#) ↗

In the Clinic

Skeptics Retreat Cells replace organ function

DAVID HUMES, M.D., HAS PUT UP WITH a lot of skepticism over the years from people who didn't believe that ordinary cells — even a few million of them — could replace the function of an entire complex organ like the human kidney.

Now, after a decade of work, Humes' persistence is paying off. What was once just a vague concept of a "bioartificial kidney" is now a reality that is saving lives of critically ill patients. A biotechnology company, Nephron, is funding the clinical trials required for FDA approval to make Humes' renal tubule assist device, or RAD, commercially available. The company also is tackling the challenge of how to mass-produce, store and ship a device made of living cells.

"We have proved the concept that organ replacement therapy may be achievable in acute and chronic organ failure," says Humes, a professor of internal medicine. "These are just the first glimpses of how we may be able to impact the natural history of disease in a substantial way."

Each year, nearly 200,000 people in the United States develop acute renal failure — also called acute kidney injury. This complex, life-threatening disorder occurs when injured kidneys shut down. Although some patients can recover, the mortality rate for AKI has remained between 50 percent and 70 percent for the past four decades.

Shock, dehydration, infection, certain medications and trauma can destroy the kidney's renal proximal tubule cells and trigger acute kidney injury.



David Humes examines the bioartificial kidney developed in his lab.

The body can repair renal proximal tubule cells and grow new ones, but the process takes 10-14 days. During this time, patients are vulnerable to a vicious spiral of events that can lead to multiple organ failure and death.

Conventional treatment for AKI has been dialysis — an extracorporeal (outside-the-body) process that filters

impurities and waste products from the blood. But filtering blood isn't what renal proximal tubule cells do. They reabsorb vital nutrients and fluids lost during filtration, and they have important metabolic, endocrine and anti-inflammatory functions that can't be duplicated by an inanimate membrane in a kidney dialysis machine.

The renal tubule assist device is a 10-inch-long cylinder containing thousands of hollow fibers lined with millions of hollow fibers lined with millions of live human proximal tubule cells. The cells are grown from progenitor cells harvested from kidneys donated for transplant, but unable to be used. Inside the RAD, the cells seem to carry out the same functions they would in a living kidney.

“The idea behind it was simple,” Humes says. “If the primary problem in AKI is damaged renal proximal tubule cells and you can replace the function of those cells, you can change the patient’s poor prognosis.”

In a recent phase II clinical trial involving 58 critically ill patients with acute kidney injury at 12 medical centers nationwide, the 28-day mortality rate for patients treated with conventional dialysis was 66 percent. Patients treated with the RAD, in addition to dialysis, had a 33 percent mortality rate. Within the first 180 days following therapy, the mortality rate for patients receiving the combination therapy was reduced by about 50 percent.

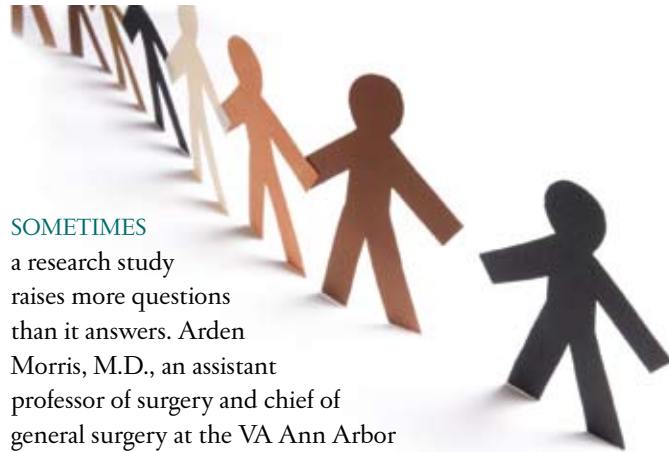
Humes says his next goal is to miniaturize the RAD and make a portable device which can be worn by people with chronic kidney disease, a condition that affects nearly 17 percent of Americans. Humes already has developed a prototype — about the size of a personal digital assistant — that contains 10 times more RPT cells and can be frozen and stored.

Humes also is exploring how cell therapy technology could be adapted for other types of organ failure.

—KIMBERLEE ROTH AND SALLY POBOJEWSKI

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Disparities Not All Black and White



SOMETIMES

a research study raises more questions than it answers. Arden Morris, M.D., an assistant professor of surgery and chief of general surgery at the VA Ann Arbor Healthcare System, was surprised by the results of her recent research on racial disparities in survival from rectal cancer.

Morris knew that long-term survival rates for black patients following rectal cancer surgery were 14 percent to 20 percent lower than they were for white patients. Several possible reasons for the difference, including less access to specialists, had been suggested by other researchers, but no one knew for sure.

To find the answer, Morris and her collaborators pulled data from a cancer registry maintained by the National Cancer Institute. They analyzed information on 2,582 whites and 134 blacks ages 66 and older who had been diagnosed and treated surgically for stage II or stage III rectal cancer.

The research team found no significant difference between the percentages of black and white patients who consulted a medical oncologist or radiologist after rectal cancer surgery. But there were big differences in what happened after patients left the physician’s office.

While 70 percent of white patients in the study went on to receive chemotherapy, only 54 percent of black patients did so. Only 74 percent of blacks were treated with radiation therapy, as opposed to 83 percent of whites. Adjuvant chemotherapy and radiation increase survival rates by about 20 percent in patients with rectal cancer, so the fact that fewer black patients receive these therapies is cause for concern.

“Now we know that the initial visit with an oncologist is not the barrier to treatment,” says Morris. “Our next step is to try to understand the human factors that contribute to this discrepancy.” —SP

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In the Clinic

One-Two Punch for Heart Health

WHEN IT COMES TO LOWERING BLOOD PRESSURE and the associated risk of heart attack, stroke and other cardiovascular events, it appears that two drugs are definitely better than one. So much better, in fact, that a clinical trial comparing the effectiveness of two-drug regimens in 10,700 patients was stopped ahead of schedule.

The study's clear winner was a two-drug combination tablet containing an ACE inhibitor and a calcium channel blocker, or CCB. Patients with hypertension who took this combination had 20 percent fewer cardiovascular-related events than volunteers who took an ACE inhibitor combined with a diuretic. Both drug combinations lowered blood pressure to recommended levels in 80 percent of study participants.

"These results demonstrate the superiority of the ACE/CCB combination treatment for reducing cardiovascular morbidity and mortality," says Kenneth Jamerson, M.D., a professor of internal medicine in the Cardiovascular Center.

Current clinical care guidelines recommend starting hypertension patients on just one drug, usually a diuretic, and adding other drugs only as needed. According to Jamerson, the study results indicate it's time to change those guidelines. —SP

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Cornea Count Increases

MANY PARTS OF THE HUMAN BODY DETERIORATE IN OLD AGE, but the cornea is not one of them. A nationwide study of patients who received corneal transplants found that corneas from older donors worked just as well as those from younger donors.

The cornea is a piece of clear, dome-shaped tissue that covers the front of the eye to protect it and help focus light. In the United States, more than 39,000 donated corneas are transplanted every year.

Kellogg Eye Center was one of 80 sites that participated in the Cornea Donor Study. For five years, researchers followed 1,101 people who received corneal transplants to monitor how long their new corneas continued to function and remain clear.

The transplant success rate was 86 percent. The success rate was the same for corneas from donors ages 12 to 65 as it was for corneas from donors ages 66 to 75, says Alan Sugar, M.D., a professor of ophthalmology and visual sciences at the Kellogg Eye Center.

Based on the study results, the National Eye Institute now recommends that eye banks expand the cornea donor pool to include donors up to 75 years old. Current guidelines limit the pool to people 65 and younger. Opening the donor pool to older people could increase the potential supply of corneas available for transplant by 20 percent to 35 percent, according to the NEI. —SP

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Health Briefs

Survival rates for children with acute lymphoblastic leukemia, the most common type of childhood cancer, have never been higher. Thanks to more effective therapies, 87 percent of five-year survivors now live to adulthood. But survival comes with a price: At least half the survivors still struggle with chronic medical conditions — a result of chemotherapy or radiation used to treat the disease. U-M researchers say leukemia survivors, especially those who received radiation or survived a relapse, should have long-term follow-up.

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The Association for the Accreditation of Human Research Protection Programs recently granted full accreditation to the University of Michigan. AAHRPP accreditation indicates that the University meets or exceeds all state and federal regulations for safe and ethical conduct of research with human subjects. U-M currently has nearly 5,000 active research projects involving human participants.

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Clogged carotid arteries in the neck increase the risk of a stroke. But is it safer to remove the built-up plaque with surgery or insert a mesh tube called a stent to open the blocked artery? In a study of high-risk patients, U-M researchers found there's no difference. Patients treated with surgery were just as likely to have a heart attack, stroke or die within three years as a matched group of patients treated with stents.

—SP [MORE ON THE WEB](#) ↗

More high school and college students are popping pills and downing energy drinks to stay alert and handle the stress of final exams. Studies have reported the use of stimulant drugs in up to 35 percent of college students and as many as 10 percent of high school students. U-M researchers warn that abuse of stimulants and energy drinks can have serious medical consequences — including anxiety, depression, irritability, high blood pressure and stroke.

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Robert Kelch (M.D. 1967, Residency 1970), U-M executive vice president for medical affairs and CEO of the Health System, and his wife, Jeri, listen as bells in Burton Tower toll for six minutes to honor the six Survival Flight and transplant team members killed in an airplane crash on June 4, 2007. The ceremony was one of several campus events held on June 4 to commemorate the one-year anniversary of the tragedy. “Virtually every day since that horrific moment, I think about our lost team,” Kelch said. “I think about what they stood for, what they achieved and what they sacrificed.”

In the School

Opening Michigan to the World

Health education goes online

AN AMBITIOUS PROJECT IS BEING

led by the Medical School to convert the University of Michigan's pre-clinical health teaching materials into online educational resources. The goal of the pilot project is to decrease disparities in access to health education resources in developing countries. Lack of access, and the resulting scarcity of trained health care providers, is at crisis proportions in many parts of the world.

Working closely with the University of Cape Town and the University of Ghana in Africa, as well as with the U-M schools of Public Health, Dentistry and Information, the Medical School is converting existing educational materials into an online format. They will be available not only to partner institutions in Africa, but also to health science schools around the world to help educate health professionals. Other health science schools at Michigan, including nursing, pharmacy, kinesiology and social work, also are supporting the project.

"This is an exciting opportunity for our university," says James O. Wooliscroft, M.D., dean of the Medical School. "This program provides the opportunity for U-M health science schools and the School of Information to collaborate in an innovative, comprehensive approach to improve educational opportunities for health care providers globally, and to help



improve medical education in developing countries."

Known as Open.Michigan, the pilot is unique from similar projects undertaken at other top universities by virtue of its use of dScribe, a low-cost method developed by the School of Information to convert educational materials into online educational resources. The dScribe method involves close collaboration among students, faculty and staff to assess the quality of resources and to clear intellectual property in course materials. A future effort is expected to include educational materials beyond the health sciences.

Funded largely by a grant from the William and Flora Hewlett Foundation, additional support for the pilot comes from the U-M, the Open Society Institute, and the Foundation for Advancement of International Medical Education and Research.

Open education resources comprise full courses, course materials, modules, textbooks, videos, tests, software and other educational tools, materials or techniques. These resources are in the public domain or have been released under a Creative Commons intellectual property license.

—BRUCE SPIHER AND RICK KRUPINSKI

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2008 Entering Class

The paperwork's been completed, reviewed, evaluated and filed. E-mail exchanges, phone calls, visits and interviews are all part of admissions history now, as are the tough decisions the Medical School and prospective students faced. August 4 marked the beginning of classes for this year's entering medical students who will graduate with M.D.s as the Class of 2012. The following statistics provide background on the newest members of the U-M Medical School.*

Meanwhile, the process for 2009's incoming students already is underway, with 2,479 applications received as we went to press; 150 applicants have been offered interviews. The first offer of admission for next year's class will take place in mid-October. The school's "transparent" admissions process makes information accessible to applicants every step of the way. This open approach allows those who apply to

learn early and often where they stand in their bid to study medicine at Michigan, relieving some of the anxiety in this monumental — and monumentally important — process. —RK

Admissions Summary

Applicants	5,818
Interviewed	744
Class Size	170
Class Average GPA	3.74
Class Average MCAT	11.63

Class Composition

Male	47.6%
Female	52.4%
M.D./Ph.D. students	8
Average Age	23.2 (Range 20–35)

Class Geography

Michigan residents	78 (45.9%)
Non-residents	92 (54.1%)
States represented	30

California	14
Illinois	10
Massachusetts	9
New York	7
Florida	6
Pennsylvania	5

Most Represented

Undergraduate Schools

Michigan Institutions Represented	12
U-M Students	43
Harvard	12
Stanford	6
Johns Hopkins	5

Undergraduate Field of Study

Biology and Biomedical	46.4%
Chemistry/Biochemistry	12.4%
Humanities	3.6%
Engineering	4.2%
Other Science	22.6%
Business/Economics	4.2%
Other	5.4%

* AS OF JULY 29, 2008



Medical Education Day annually highlights educational innovations throughout the U-M Medical School. At this year's event, held June 10 at the Towsley Center, the plenary speaker was William C. McGaghie, Ph.D., professor and associate director of the Office of Medical Education and Faculty Development for the Feinberg School of Medicine at Northwestern University. Interdisciplinary health science education was the topic of the plenary session; a panel discussion followed McGaghie's remarks.