ABOVE THE HURON
News and research from the Medical School

Bioengineering the Heart, Piece by Piece

It looks like heart muscle and beats like heart muscle, but this small patch of pulsing cardiac tissue didn't come from a living animal. It was created by researchers in the U-M Artificial Heart Laboratory. Their ability to grow bioengineered heart muscle from cardiac cells in the lab represents a major step toward the long-term goal of creating replacement parts for damaged human hearts.

Heart attack survivors could one day have patches of laboratory-grown muscle implanted in their hearts to replace areas that died during the attack.

"Tissue engineering is a rapidly evolving field, and cardiovascular tissue is one of the most exciting areas, but also one of the most challenging," says Ravi Birla, Ph.D., who directs research in the Cardiac Surgery Artificial Heart Laboratory. "Although tremendous technological challenges remain, we are now at a point where we can engineer first-generation prototypes of all cardiovascular structures."

This means that heart attack survivors could one day have patches of laboratory-grown muscle implanted in their hearts to replace areas that died during the attack. Children born with defective heart valves could get new ones that grow permanently in place, rather than having to be replaced every few years. And people with clogged or weak blood vessels might get a "natural" replacement grown in a tissue incubator called a bioreactor.

While it will be years before bioengineered heart muscle can be used in human beings, U-M scientists have started experiments to transplant it into the hearts of rats with heart attack damage to see if the new tissue heals the damage.

Among the hurdles still to be overcome: determining which types of

Photo: Scott Galvin

Ravi Birla with Louise Hecker, a graduate student in the Section of Cardiac Surgery. Birla and Hecker are senior author and lead author, respectively, on the paper, "Engineering the heart piece by piece: state of the art in cardiac tissue engineering," published in the March 2007 issue of *Regenerative Medicine*.

cells hold the most potential and finding the best way to grow those cells to form viable cardiac tissue that is strong, long-lasting and structured, at a cellular level, like natural tissue.

U-M scientists and biomedical engineers work together in the Artificial Heart Laboratory to compare the effectiveness of different platforms used to engineer functional heart muscle. With the right growing conditions, they can encourage cardiac muscle cells to begin producing the molecules they need to communicate and connect with other cells, and to generate the extracellular matrix or scaffold that supports cells in tissue.

"We're interested in creating models of the different components of the heart one by one," says Birla. "It's like building a house – you need to build the separate pieces first. Once we understand how these models can be built in the lab, then we can work toward building a bioengineered heart."

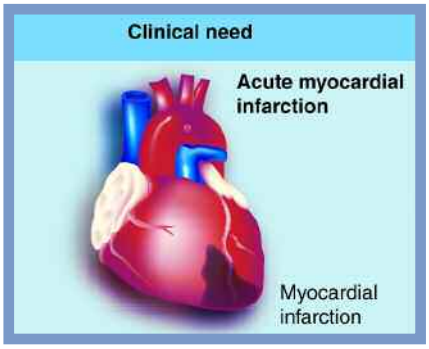
The U-M is applying for patent protection on its new bioengineering technology and is looking for a corporate partner to help bring this technology to market.

—Kara Gavin and Sally Pobojewski

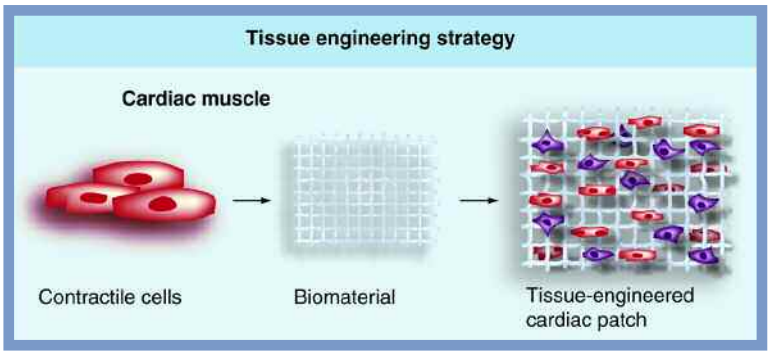
For an expanded version of the story:
www.med.umich.edu/opm/newspage/2007/enginheart.htm

www.med.umich.edu/opm/newspage/2006/behm.htm

A Patch for Damaged Heart Muscle



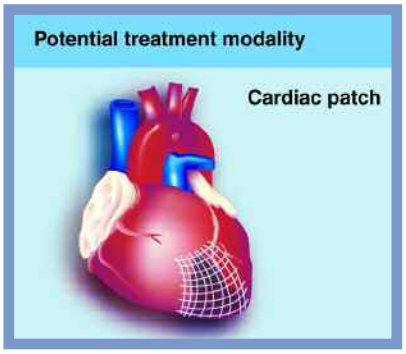
When plaque deposits form inside coronary blood vessels, they can restrict the flow of blood to an area of heart muscle, which can cause a myocardial infarction, or heart attack. Lacking oxygen and nutrients from blood, that part of the heart muscle will die (dark area). This weakens the heart's ability to pump blood efficiently.



To repair the damaged heart muscle, U-M researchers take muscle cells from somewhere else in the animal's body and remove immature satellite cells from the muscle sample.

The satellite cells are placed on a porous biodegradable scaffold to help them grow into the specific size and shape required.

The cells are grown inside a bioreactor that simulates conditions inside the body.



When the tissue-engineered patch is ready, researchers implant it over the damaged heart muscle. As muscle cells in the patch grow, they fill in and become part of the animal's heart, restoring its normal pumping ability.

Adapted from *Regenerative Medicine 2* (2), 125-144 (2007) with permission of Future Medicine Ltd.

Landmark Gift to the U-M Health System: $50 Million for Cardiovascular Center

In June, the Cardiovascular Center received an extraordinary gift supporting its innovative model of patient care and emphasizing and rewarding cooperation, excellence and measurable results in each area of the center's operations: clinical care, research and education. The benefactor, who wishes to remain anonymous, believes the model could provide a pattern for all types of health care facilities in the future.

The donor and the UMHS jointly established benchmarks for customer satisfaction, collaboration among scientists and physicians, clinical outcomes, research contributions, and excellence in education. Of the gift, $25 million will be paid over the next 10 years; another $25 million will be paid when the center meets the benchmarks. If the center receives the entire $50 million, it will be the largest gift ever made to the Health System and the second-largest to the U-M.

—Kara Gavin

For more information on the gift and the Cardiovascular Center:
www.med.umich.edu/opm/newspage/2007/cvcgift.htm

Photo: Scott Galvin

Kathleen Cho and Ronald Buckanovich

Revealing Ovarian Cancer's Deadly Secrets

When it comes to ovarian cancer, any progress is good news. Since ovarian cancer produces few or no symptoms during its early stages, 70 percent of patients aren't diagnosed until after the tumor has grown or spread to other parts of the body.

Scientists in the Comprehensive Cancer Center are trying to give physicians new diagnostic and treatment tools to help their patients with ovarian cancer. They are targeting genes responsible for tumor cell signaling and the growth of new blood vessels that feed the growing tumor. Understanding how these genes work could provide clues to ovarian cancer's deadly secrets.

A research team directed by Kathleen R. Cho, M.D., a professor of pathology and of internal medicine, is focusing on two defective cell-signaling pathways that lead to ovarian endometrioid adenocarcinoma, the second most common type of ovarian cancer.

"In the last 30 years, we haven't done a lot to improve the survival of ovarian cancer patients," Cho says. "This study has the potential to improve our understanding of early ovarian cancer."

Researchers in Cho's lab analyzed gene mutations and signaling pathway defects found in human ovarian tumor cells, and then created a strain of genetically engineered mice with the same defects to see if ovarian tumors would develop. In all the mice altered to possess both pathway defects, ovarian tumors developed rapidly and often metastasized.

Currently, Cho is using the mice developed in her lab for preclinical testing of a drug called Rapamycin to see if it can inhibit the defective cell-signaling systems involved in ovarian endometrioid adenocarcinoma.

Ronald Buckanovich, M.D., Ph.D., an assistant professor of internal medicine and of obstetrics and gynecology, is attacking ovarian cancer on a different front. He has identified more than 70 biomarkers that are found only in the cells of blood vessels running through ovarian tumors. By analyzing the biomarkers, Buckanovich and other scientists were able to identify genes that are active in tumor vascular cells.

"When these genes are highly expressed, we suspect it may be a sign of a tumor that's able to grow blood vessels more efficiently and therefore is more aggressive," Buckanovich says.

If he can prove that these markers are specific to ovarian tumors, Buckanovich believes it may be possible to develop drugs that target the blood vessels and strangle the tumor.

—Nicole Fawcett and Anne Rueter

For an expanded version of the story:
www.med.umich.edu/opm/newspage/2007/ovarian.htm

www.med.umich.edu/opm/newspage/2007/ovariancancer.htm

Is the Chemo Working?

Researchers at the Comprehensive Cancer Center have developed — and are currently testing in mice — a new technique that uses magnetic resonance imaging, or MRI, to measure the effectiveness of chemotherapy for prostate cancer that has spread to the bones. Currently, physicians have no way to tell whether or not bone tumors are responding to therapy.

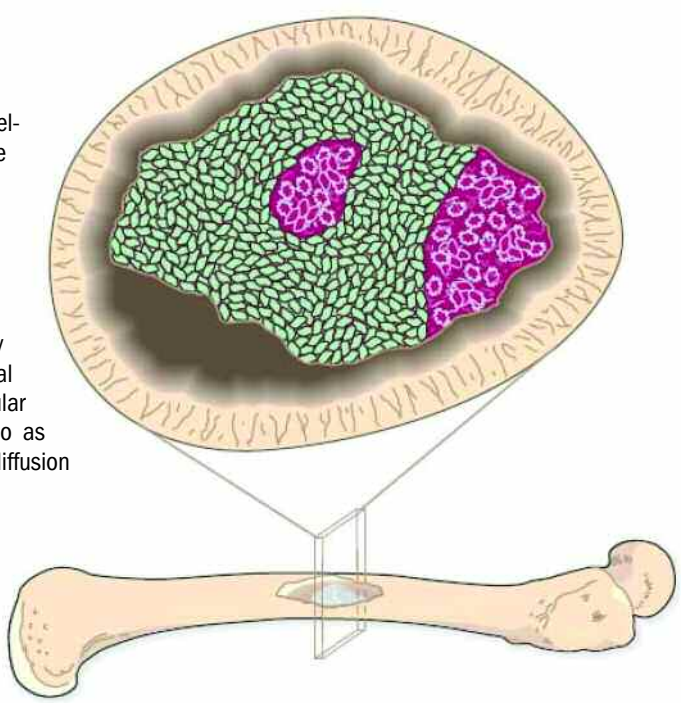
The imaging technique uses special software to track the movement of water through cells in the tumor. It was developed by Brian D. Ross, Ph.D., a professor of radiology and of biological chemistry, and other scientists in the Cancer Center's Molecular Imaging Program. Tumor cells slow the movement of water, so as those cells die from the effects of chemotherapy, water diffusion increases.

Functional diffusion map technology, as the technique is known, could be used to indicate if a tumor is shrinking, allowing patients to switch to an alternative therapy if a treatment isn't working.

—Nicole Fawcett

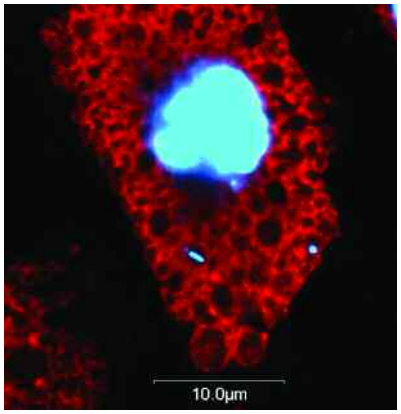
For an expanded version of the story:
www.med.umich.edu/opm/newspage/2007/prostatecancer.htm

For patient information on prostate cancer:
www.cancer.med.umich.edu/cancertreat/urologiconcology/prostate_cancer.shtml



This image of a tumor in mouse bone is based on data from magnetic resonance imaging scans of the bone taken before and after chemotherapy to shrink the tumor. Using software developed at the U-M Cancer Center, scientists can map the diffusion of water through cells in the tumor. Green areas indicate portions of the tumor that did not respond to chemotherapy.
Illustration: Brian D. Ross, Ph.D., U-M Comprehensive Cancer Center

Bacteria Invade Cells, Trigger Immune Response from Within



A mouse macrophage (cytoplasm in red, nucleus in blue) infected with bacteria (small blue elongated *bacillus*).

For years, scientists believed that when bacteria invade the body, they activate an immune response by binding to receptors on the surface of immune cells called macrophages — the body's front-line defense against infection.

Now, a U-M research team led by Gabriel Nunez, M.D., the Paul H. de Kruif Professor of Pathology, has found that invading bacteria also can slip inside macrophages and trigger the immune response by activating a protein called cryopyrin found in fluid inside the cell. Cryopyrin is implicated in the development of several inflammatory syndromes characterized by recurrent fever, skin rash and arthritis.

This research gives scientists new targets and pathways for future vaccine development, as well as for drugs designed to block the body's inflammatory response in rheumatoid arthritis and some other autoimmune diseases.

—Anne Rueter

For an expanded version of the story:
www.med.umich.edu/opm/newspage/2007/microbes.htm

Skepticism Gives Way to Remarkable Results for Surgical Procedure

Thirty years of experience with a complex surgical procedure called transhiatal esophagectomy has reduced mortality and complications and given the U-M Health System one of the best patient safety records with the procedure in the country.

First developed by Mark Orringer, M.D., now a professor and head of thoracic surgery, the operation is used to treat esophageal cancer and other conditions requiring removal of the esophagus. Since the U-M procedure does not involve opening the chest to remove the esophagus, it is less difficult for patients and generates fewer complications than a traditional thoracotomy.

Transhiatal esophagectomy was not warmly received by thoracic surgeons when Orringer first introduced it, but after 2,000 procedures, U-M's mortality rate is now just 1 percent, and complication rates have dropped from 32 percent in the early years to between 1 percent and 2 percent more recently. "We have the most comprehensive experience with this operation ever reported," Orringer says.

—Nicole Fawcett

Photo: Scott Galvin

Donald Rockefeller enjoys breakfast in his hospital room while visiting with Mark Orringer, who performed Rockefeller's transhiatal esophagectomy surgery just five days earlier.

Vaginal Delivery and Organ Prolapse: Is There a Connection?

Some women are encouraged to deliver their baby by an elective Caesarean section, because their doctors worry that a vaginal delivery will lead, later in life, to a condition called pelvic organ prolapse.

Photo: Jupiterimages/Brand X/Pete Barrett

Prolapse occurs when the bladder, uterus or lower bowel falls from its normal position in the body into the vaginal area. A common effect of the condition is urinary incontinence. Every year, more than 200,000 women have surgery to correct prolapse and other pelvic floor disorders.

Whether vaginal delivery actually causes this condition has been hotly debated in the medical community. In a recent study, Medical School researchers found a strong connection between muscle damage that can occur during vaginal deliveries and pelvic organ prolapse. Rates of muscle injury were particularly high when forceps were used to assist delivery, according to John O.L. DeLancey, M.D., the Norman F. Miller Professor of Obstetrics and Gynecology.

Fifty-five percent of women in the study with prolapse were found to have major damage to the levator ani muscle, which supports the bladder and uterus, compared to just 16 percent of women without prolapse. When women were asked to contract their pelvic muscles, the muscles were 40 percent weaker in women with prolapse.

However, DeLancey cautions against using the findings to support more elective C-sections. He says study results should be used to help identify how women are injured during vaginal birth in an effort to make it safer.

—Katie Gazella

For an expanded version of the story:
www.med.umich.edu/opm/newspage/2007/prolapse.htm

For patient information on pelvic organ prolapse:
www.med.umich.edu/1libr/aha/umpelvicpro.htm

Vitamins to Prevent Hearing Loss?

If a daily dose of extra vitamins could protect you from noise-induced hearing loss, would you take it? Scientists at the U-M Kresge Hearing Research Institute are convinced there are lots of people who'd be interested – especially soldiers, musicians, pilots, construction workers or anyone who wants to protect their hearing from the daily din of modern urban society.

Josef M. Miller, Ph.D., a professor of otolaryngology and former director of the institute, and Colleen Le Prell, Ph.D., a former research investigator there, tested a combination of high doses of vitamins A, C, E and magnesium in a preclinical animal study and found it to be very effective at preventing permanent noise-induced hearing loss. The animals had prolonged, close-range exposure to sounds as loud as a jet engine during take-off.

Convinced that the right combination of antioxidants and a vasodilator can effectively prevent this type of noise-induced inner ear damage, Miller launched a U-M start-up company called OtoMedicine to test and market the vitamin-and-magnesium formulation for use in people.

Clinical trials of a hearing-protective tablet or snack bar are scheduled to begin in Sweden this summer, according to Miller, co-principal investigator with colleagues at the Karolinska Institute. The doses of the commonly used dietary supplements to be tested in the clinical study are known to be safe for human consumption. If results show that the formulation is effective at preventing hearing loss in people, Miller says a product could be on the market within two years.

–Anne Rueter

For an expanded version of the story: www.med.umich.edu/opm/newspage/2007/hearingloss.htm

For patient information about hearing loss: www.med.umich.edu/1libr/aha/aha_noishear_crs.htm

Photo: Scott Galvin

Josef Miller

Obesity in Girls Linked to Early Puberty

The growing national rate of childhood obesity appears to be contributing to early puberty in girls, according to researchers at the U-M C.S. Mott Children's Hospital.

"Our study indicates that increased body fatness is associated with earlier onset of puberty," says pediatric endocrinologist Joyce Lee, M.D., an assistant professor of pediatrics and communicable diseases and a member of the Child Health Evaluation and Research Unit.

In a study of 354 American girls ages 3 to 12, Lee and the research team found that a body mass index score in the 85th percentile or above in girls as young as age 3, and large increases in scores between age 3 and first grade, were associated with early breast development and menstruation.

According to Lee, early puberty can lead to a higher incidence of behavioral problems, early alcohol use and sexual intercourse, and increased rates of adult obesity and reproductive cancer.

–Krista Hopson

For an expanded version of the story: www.med.umich.edu/opm/newspage/2007/puberty.htm

Resources for parents with overweight children: www.med.umich.edu/1libr/pa/pa_blobesit_pep.htm

Students Award Pharmaceutical Policy an "A"

In 2003, the Health System was one of the first institutions in the U.S. to limit interactions between staff and pharmaceutical representatives. It was also among the first to eliminate, in 2002, the use of drug samples in its clinics and hospitals.

Now, the American Medical Student Association has recognized the Health System for its policy restricting drug representative access. In its first assessment of medical schools and affiliated medical centers, only the U-M, Stanford University, the University of California-Davis, the University of Pennsylvania and Yale University received an "A" on the association's scorecard.

–Kara Gavin