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N.C. researcher part of trio that will get Nobel Prize for medicine

By Steve Hartsoe
The Associated Press

CHAPEL HILL — As a child growing up in England, Oliver Smithies read the comics. One strip had an inventor, and Smithies decided then that’s what he wanted to be.

A path that began on the funny pages took Smithies from his home in Yorkshire to Oxford University. It took him across the Atlantic to a medical research lab at the University of Toronto, where he began his research into genetics. It led him to the University of North Carolina researcher learned of his next destination in a pre-dawn phone call Monday. He’s headed to Sweden to accept the 2007 Nobel Prize in medicine.

“My work was never toward getting the Nobel Prize,” Smithies told The Associated Press over a cup of tea at his lab a few hours after the Nobel committee called with the news. “It was solving a problem, and enjoying the solution.”

Smithies, 82, is an excel-

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ience professor of pathology and laboratory medicine at North Carolina's school of medicine, where for the past 19 years he has focused on using gene therapy to study hypertension and other genetic disorders, including sickle cell disease.

"I've always wanted to help with the common diseases, not the rare diseases, working in relation to hypertension, for example," Smithies said.

Smithies shared the prize with Mario R. Capecchi, 70, of the University of Utah in Salt Lake City, and Sir Martin J. Evans, 66, of Cardiff University in Wales. Their technique, using embryonic stem cells of mice, allows researchers to produce offspring with altered genes, and the widely used process has helped scientists study heart disease, diabetes, cancer, cystic fibrosis and other diseases.

"Gene targeting has pervaded all fields of biomedicine. Its impact on the understanding of gene function and its benefits to mankind will continue to increase over many years to come," said the citation for the $1.54 million prize.

Moments after the 5 a.m. wakeup call from Sweden, Smithies called the Nobel "very gratifying" and said after working on the research for more than 20 years, it's rather enjoyable being recognized at this level.

"I'm still feeling sleepy," he admitted.

The accolade adds to Smithies' lengthy list of honors. They include the 2001 Albert Lasker Award for basic medical research, which is often called "America's Nobel," and his election to the national Institute of Medicine in 2003. In January, a month after accepting the Nobel, Smithies will receive the Genetics Society of America's Thomas Hunt Morgan Medal for lifetime contributions to the science.

"Oliver Smithies' innovations have revolutionized genetic research and advanced the effective treatment of many diseases, and millions of people worldwide have better and longer lives because of the talent and determination he has brought to his work," said North Carolina Chancellor James Moeser.

"For decades, he has embodied the very best of academic research and humanity through his modesty, good humor, creativity and love of invention," Moeser said. "Through his example, hundreds of students and colleagues have learned how to help the world through research."

Smithies shares a small office at North Carolina with his wife, Nobuyo Maeda, the Robert H. Wagner distinguished professor of pathology and laboratory medicine at North Carolina. There was no immediate celebration in the lab, although the university planned to fete Smithies at a press conference later Monday.

"I hope this can inspire students to enjoy their work while they're doing it, because most of their experiments won't work," he said.

The medicine prize is the first of the six prestigious awards to be announced this year, and Smithies said he hopes winning the Nobel Prize will make it easier to secure funding for other work.

"I hope it won't change" my life, Smithies said. "I enjoy what I do."

On the Net:

Nobel Prizes: http://nobel-prize.org

Associated Press writer Bernard McGhee in Atlanta contributed to this report.
ECU player's status up in the air after arrest

By Nathan Summers and Jimmy Ryals
The Daily Reflector

An East Carolina University wide receiver's playing status is in question after his arrest Sunday.

Michael Deval Hickman Jr., 22, was arrested on Stratford Road around 3 a.m. Sunday on disorderly conduct charges.

ECU head coach Skip Holtz said he had not made a decision on his playing status. Hickman reportedly practiced with the team Sunday night.

Holtz said he was still gathering information on the incident.

"I sat down and talked to Michael on Sunday, but I haven't made a decision yet," Holtz said. "There are

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two sides to every story, and I don't want to make a decision based on one side of it."

Hickman has a Nov. 21 court date scheduled for the disorderly conduct charge. He is also due in Pitt County District Court on Jan. 21, 2008, on a charge of driving while impaired. The charge stems from a Jan. 1, 2005, incident. Other charges filed on the same occasion — driving after consuming alcohol, possessing an open container after consuming alcohol and driving without a license in possession — were later dropped.

Four years ago, Hickman was charged with breaking or entering of a motor vehicle in connection with a May 2003 incident. He later received a prayer for judgment.

Hickman, largely used as a special teams player, made two receptions for 43 yards — including one for 31 yards — in Saturday night's 52-28 win over the University of Central Florida. He has three catches for 59 yards and five carries for 21 yards in his career.

A walk-on from Greenville, Hickman played prep football at D.H. Conley High School.

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Public Forum

Celebrating National Midwifery Week

The American College of Nurse-Midwives is celebrating National Midwifery Week through Saturday. This week, midwives and the women they serve may reflect on their experiences and midwifery’s contribution to women’s health care, from attending births to well-woman care.

There are more than 10,000 nurse-midwives in the United States and nearly 200 in North Carolina. In our state, certified nurse-midwives are licensed by a nurse-midwifery joint committee and practice in association with a collaborating physician. Their goal is to decrease the rates of maternal and infant morbidity and mortality and improve the lives of mothers and families.

ECU School of Nursing’s graduate nurse-midwifery operation, started in 1991, is the only nurse-midwifery program in North Carolina and one of the few in the U.S. that offers online education. There are 110 alumni of this program, many of whom practice in rural North Carolina areas.

Nurse-midwives have been a vital part of the School of Nursing and women’s health in Greenville for 16 years. At the ECU School of Nursing, nine nurse-midwifery faculty teach undergraduate and graduate nursing students and several have nationally funded research projects. At ECU, five nurse-midwifery faculty provide prenatal and well-woman care at Pitt County Health Department and several attend births at PCMH.

Nurse-midwives also precept medical students and interns from Brody School of Medicine in normal OB/GYN clinicals and see patients at ECU Women’s Physicians. Six Greenville nurse-midwives provide prenatal care and labor support to low-risk pregnant clients and attend births in the hospital with the backup of collaborating obstetricians.

The Nurse-Midwifery Week theme, “Women, for a Lifetime,” celebrates the role midwives play in women’s lives. Please join us in celebrating nurse-midwifery services in our area and ECU’s nurse-midwifery option, a vital part of the School of Nursing and ECU’s academic community.

D. ELIZABETH JESSE
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Greenville
UNC scientist wins Nobel

Smithies shares prize in medicine

BY JANE STANCILL
STAFF WRITER

CHAPEL HILL — Sunday was an ordinary day for Oliver Smithies, 82. He flew his glider over Chapel Hill, took his wife to lunch and crafted a response to a committee that had denied his latest grant proposal.

On Monday, the scientist was awakened at 5 a.m. by a call from Stockholm, Sweden. He had won the Nobel Prize in medicine.

Smithies, a British-born professor of pathology and laboratory medicine at UNC-Chapel Hill, shares the prize with Mario Capecchi of the University of Utah's Howard Hughes Medical Institute, and Sir Martin Evans of Cardiff University in Wales.

The three developed methods for manipulating genes and creating designer mice now used in labs all over the world. The work accelerated the field of genetic medicine and laid the foundation for today's research into gene therapy. It is used to study human diseases such as cystic fibrosis, cancer and heart disease.

A UNC-CH faculty member for 19 years, Smithies began his work at the University of Wisconsin in the 1980s. The three scientists worked independently but shared information. Gene-targeting allowed the researchers to use "knock-out mice," in which genes were removed to understand their effects. The first mouse with manipulated genes was born in 1989, and since then, more than 10,000 genes in mice have been

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studied using the technique, the Nobel citation said.

Smithies spent Monday morning at his lab, where he was bugged by calls from reporters in Russia, France and Germany. He fielded a call from the Swedish Embassy that included an invitation to appear at the White House. Colleagues brought a bouquet of coral roses and yellow lilies. They threw together a party, but Smithies could barely get off the phone to attend. A yellow sticky note from his assistant said, "Ice cream is melting... Come!"

"I feel rather peaceful," he said in an interview in his small, cluttered office, where little toy mice perch on his bookshelf alongside boxes of mint tea bags. "I've been working at the bench for more than 50 years, and it's nice to find that people appreciate what you've done. It feels like what a lot of people have mentioned — a capstone on one's career."

Later, he was greeted by the cheers of scientists, doctors and students at a balloon-decorated atrium in UNC's Lineberger Cancer Center, where carrot cake was served in his honor at a reception.

"There is no doubt that this work will lead to new therapy in virtually every disease that has a genetic basis," said Dr. Etta Pisano, a vice dean in UNC-CH's medical school. "That is really not overstating the importance of this discovery."

"A nice little glow" At a news conference, Smithies' postdoctoral fellows and lab technicians crowded in with digital cameras. He was modest, saying he gets "a nice little glow" whenever he opens a journal and sees that his methods — now taken for granted — are being used by scientists across the globe.

Smithies' colleagues had expected his Nobel Prize for years. In 2001, he and his fellow Nobel winners won the Albert Lasker Award for Basic Medical Research, often a Nobel precursor. "People at various times have said, 'You're nominated,' " Smithies said, "and I got used to the fact that nothing ever happened."

Peter Agre, a 2003 Nobel winner in chemistry and vice chancellor for science and technology at Duke University, said he is humbled by Smithies' work. "That man is a real scientist," Agre said. "I consider myself a science wannabe in comparison."

Dr. Stuart Bondurant, former UNC-CH medical dean who recruited Smithies, said, "You can't believe his warmth, magni-

Smithies told the UNC-CH crowd he had no inclination to retire. "I've always said if I were to die somewhere, which certainly will happen, it might as well be at the bench because that's where I'm happy."

The Nobel Prize carries a monetary award of $1.54 million. The ceremony in Sweden will be in December, but Smithies wasn't too caught up in the hoopla. His evening plans Monday? Watching baseball. "I don't have any particular desire for my life to change," he said. "It's a happy life, and we're happy together, and we enjoy our work together. Maybe it might be easier to get a little bit of money to be able to do the work because I still get my grants turned down just like everybody else."

Smithies said he'll resubmit that rejected proposal next month.

Staff writer Tim Simmons contributed to this report.

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Smithies’ work is crucial

Colleagues ‘would be years and years behind’ without it

BY TIM SIMMONS

To understand the importance of Oliver Smithies’ work, think of taking a cross-country trip without directions or a map. That’s how basic his contributions are to medical research.

“Without his work, we’d still be groping in the dark,” said Bridgid Hogan, chairwoman of cell biology at Duke University Medical Center. “We would be years and years behind.”

Smithies shared the Nobel Prize in medicine Monday for work that dates to 1985 when he was a professor at the University of Wisconsin.

Researchers knew that genes played a key role in human illnesses, but they couldn’t pinpoint the genes or mimic the illness in animals.

“Scientists were forced to study mutant animals, basically animal freak shows,” said Peter Agre, a 2003 Nobel Prize winner in chemistry.

Then Smithies developed a technique that permitted scientists to alter single, specific genes in laboratory mice. Eventually, he and others were breeding custom-made mice by genetically altering embryonic stem cells and developing them into grown animals.

The result was a leap in understanding the relationship between genes and disease. Instead of waiting to find an animal with a disease that appeared to mirror human illnesses, a “mouse model” could be created in the lab for endless study.

“The genius of this is using embryonic stem cells as a target,” said Agre, vice chancellor for science and technology at Duke University Medical Center. “Then within that target you pick one specific gene out of 30,000 or so, and you obliterate it. This sort of reverse approach allows us to study individual genes.”

Smithies, who is known also for making science accessible, has compared it to removing a steering wheel from a car. If you don’t appreciate the purpose of a steering wheel before it is removed, you can’t help but understand its function once it’s gone.

The technique has allowed researchers to make strides in understanding conditions such as cystic fibrosis, a life-threatening disease that allows a thick mucous to gather in the lungs. Richard Boucher, a leading cystic fibrosis researcher based at UNC-Chapel Hill, was among the first to approach Smithies about using mouse models to study the disease. By knocking out a single gene, scientists could mimic cystic fibrosis in mice.

“It was incredibly difficult,” Boucher said. “I think it took them three years. It is very complex.”

As expected, the diseased mice died of the same gastrointestinal problems as humans. The lungs of mice, however, were unaffected.

Discovering why a mouse’s lungs do not clog with mucous brought a new focus to research. Boucher hopes it will also bring a new drug to market within two years than can be used to treat the disease.

The science of heart disease, diabetes, cancer and hypertension — just to name a few — have all benefited.

“They give a Nobel Prize every year in medicine, and they are all very important,” Agre said. “But this is historically important. One hundred years from now people are still going to be talking about this one.”

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Blood puzzle may be solved

Duke data could aid transfusions

BY JEAN P. FISHER
STAFF WRITER

For years physicians noticed that patients who received transfusions of banked blood were more likely to die than those who got no blood. Now Duke University researchers think they know why — and how the problem may be solved.

Donated blood almost immediately begins to lose a key gas that opens up vessels so oxygen and nutrients get to starved tissues, the Duke researchers report. Without that gas — nitric oxide — the vessels stay closed, blood can’t deliver its precious cargo, and patients founder, the scientists suggest in two articles published online late Monday in the journal Proceedings of the National Academy of Sciences.

The good news is that nitric oxide can easily be put back into banked blood, restoring its ability to open vessels and transfer oxygen, the Duke scientists also report. Tests showed that blood replenished with nitric oxide successfully opened blood vessels in live dogs, doubling the flow of blood to the animals’ hearts.

If similar results can be produced in humans, the findings could have huge consequences for the way donated blood is transfused.

Dr. Jonathan Stamler, a Duke physician trained in both cardiology and pulmonology and senior author of one of the recent articles, thinks replenishing blood before transfusion — something that could be done in minutes by hospital staff — could eventually become standard procedure. About 14 million units of donated blood are given to nearly 5 million Americans each year.

“There’s a real hope that this can change practice,” said Stamler.

The American Red Cross, the nation’s largest supplier of banked blood, indicated that the Duke findings are of “considerable interest.”

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"We anticipate it may eventually lead to a better understanding of how to preserve red cell properties during storage," the Red Cross said in a statement.

Doctors unconnected to the Duke studies agree that there’s a worrisome relationship between transfusion and poor patient outcomes, which has been demonstrated in studies over the past decade. But they say a lot more research is needed before depleted nitric oxide can be confirmed as the main culprit.

The reasons patients who get transfusions do worse “aren’t well understood,” said Dr. Mark Brecher, director of transfusion medicine at UNC Hospitals in Chapel Hill. Still, he thinks the Duke researchers have opened an intriguing new area of research.

“But I think it is just part of the answer,” Brecher said. “They do not explain all of the questions about banked blood.”

It has long been understood that banked blood undergoes many biological changes that may affect patients. Stamler’s lab first described nitric oxide’s role in dilating blood vessels years ago.

But the Duke studies are the first to document the rapid loss of nitric oxide in banked blood. One study found levels of the gas begin falling within three hours of donation and plummet 70 percent within 24 hours. That suggests a link to bad outcomes.

Stamler, who led the study that tested banked blood in dogs, agreed that studies in people are needed to determine the true clinical benefit. His study looked only at how well blood with both normal and depleted levels of nitric oxide opened blood vessels. It did not look at whether opening those vessels resulted in a better clinical outcome.

Without that information, it’s hard to say what the findings really mean for patients, said Dr. Pascal “Osi” Udekwu, medical director of trauma and general surgery at WakeMed in Raleigh. Many transfusions are given either to surgical patients or those injured in accidents.

“This would be really important if they could show us an improved outcome,” Udekwu, who is also an associate professor of surgery at UNC-Chapel Hill, said of the Duke studies. “But they have not shown that correction of this single problem will make blood use any safer.”

Blood transfusion was once unquestioningly accepted as beneficial or even life-saving for patients whose blood levels drop, starving their tissues for oxygen. But that has changed over the past several years as research established a link between transfusion and increased risk for heart attack, heart failure and even death. One analysis of heart patients, published by Duke cardiologists, found that patients who had blood transfusions were about three times as likely to suffer a heart attack or die within 30 days as patients who did not have a transfusion.

Such findings initially caused physicians to speculate that problems in transfused patients might be unrelated to blood, stemming instead from the fact that they were already very ill. But the link between transfused blood and increased risk of death has since been established.

“It’s something that we struggle with in medicine that no one knows about — it’s just not in the public domain,” Stamler said. “We give millions of units, and we don’t have a good idea of who we’re benefiting.”

He hopes his research can help find more answers.

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