UNMC’s AIDS A-Team
UNMC’S AIDS A-TEAM

Four world-class researchers and a patient team up at UNMC to develop breakthroughs in HIV/AIDS treatment.

ON THE COVER:
Scientists who have investigated the AIDS virus for 30 years, now work together at UNMC. From left, Howard Gendelman, M.D.; Courtney Fletcher, Pharm.D.; Susan Swindells, M.B.B.S., and Howard Fox, M.D., Ph.D.

LOSING WEIGHT ONLINE IN RURAL NEBRASKA
A web-based intervention for weight loss and weight maintenance is designed to help women in rural Nebraska be successful.
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DNA – THE PRIMARY FRONTIER
Voyage into the building blocks of life to sequence large amounts of DNA and unravel the mysteries of cancer, heritable diseases, infectious diseases and autism.

CAN YOU TRANSLATE?
Changes in health care will occur more rapidly and reliably when teams of research translators work together to tackle major health problems.

VOICES IN THE PLAZA
WORK TO IMPROVE RESEARCH, HEALTH
Fresh solutions to health problems in the South Omaha community can be found through a partnership between UNMC and more than 90 agencies.

THE EYES HAVE IT
Rods and cones in the eyes help you read these words, but understanding how they transmit signals may lead to the cause of neurodegenerative diseases.
THE NEED FOR TRANSLATIONAL RESEARCH

The office of Vice Chancellor for Research has experienced some changes. Dr. Chris Kratochvil, assistant vice chancellor for clinical research, Dr. Ken Bayles, associate vice chancellor for basic science research, and I work toward a common goal: the expansion of translational research.

To translate research you need teams of investigators with different backgrounds and skills all focused on a particular problem or disease.

Often, the research begins in a laboratory, with cells or animals, to understand the cause, or identify new markers of disease. Animal models also can be useful to develop and test prevention or treatment strategies.

But, ultimately, successful translational research needs to be confirmed in human trials. Even when the clinical trial is successful, the research doesn’t stop.

Translating those results into a community-setting also may require research. In this issue, we give examples of basic, clinical and community-based research underway at UNMC.

Translational research often requires new technology. For example, genetics is now being used to target therapies to the individual — often called “personalized medicine.”

We know that not every person benefits from every medicine equally. ‘Next generation’ genetic sequencing, now available at UNMC, can more rapidly identify the genes that predict the response of individuals. This technology also allows scientists to rapidly sequence DNA in cancers, or families with the same condition, to find new causes or targets for treatment.

Another exciting technology is nanomedicine — creating new formulations of medications using very small particles so it can move across the skin or into the brain more easily or prevent drug resistance over time.

Translating research into the community also involves technology. Dr. Carol Pullen, with other College of Nursing faculty, use technology to conduct studies in rural communities to improve health. These same technologies are being introduced to support the delivery of health care in rural areas.

Finally, I am excited to report that UNMC continues to attract top scientists from across the country and grow research programs that are recognized around the world. In this and future issues of UNMC Discover, we will highlight some of UNMC’s research teams that directly benefit the health of Nebraska, as well as change science and health care around the world.

Jennifer Larsen, M.D.
UNMC Vice Chancellor for Research
Three decades ago, not one of the five people in this story had ever heard of the University of Nebraska Medical Center or each other. They had only one thing in common — a future that would be impacted by the HIV/AIDS epidemic.

But today they work together at UNMC — four scientists and a patient — for a better treatment, perhaps even a cure, for the deadly AIDS virus. It’s translational research at its best.

HIV was described by the Centers for Disease Control for the first time 30 years ago. Since then, the catastrophic pandemic has infected more than 60 million people worldwide and killed at least half that number. About one million people in the United States now have HIV.

What’s significant is that in a state where only 2,000 people live with HIV, UNMC is the home to a brain trust of internationally-known AIDS researchers. In spite of its low incidence of HIV/AIDS, someone in Nebraska is diagnosed with HIV every 3½ days.

“Nebraska is not ground zero for the AIDS virus, but it could be for the next best treatment,” said UNMC Chancellor Harold M. Maurer, M.D., noting that 22 percent of research funds received in the College of Medicine was for HIV/AIDS.

The four researchers — Howard Gendelman, M.D.; Courtney Fletcher, Pharm.D.; Susan Swindells, M.B.B.S., and Howard Fox, M.D., Ph.D. — work with researchers from several universities, including the University of Nebraska-Lincoln, Johns Hopkins and the University of California San Diego, to attack the disease on different fronts.

The patient, Eric Ernsberger, has experienced all the difficulties that go with the virus. Together, they are on the frontline of the disease. Here are their stories.
Dr. Howard Gendelman treated his first AIDS patient in 1980 in the Bronx before the disease was described. The man had pneumocystis carinii pneumonia (PCP), an infection that normally was associated with terminal cancer patients on chemotherapy.

“Death then came within days or weeks. There was very little we could do to treat it,” he said.

Two years later he was at Johns Hopkins School of Medicine in Baltimore, studying the slow infection of the nervous system caused by the Visna-Maedi virus, which is in the same viral class as HIV. That’s where he discovered the role an immune system cell — macrophages — play in Visna, and later in HIV. The discoveries launched his career.

As part of the immune system, macrophages destroy pathogens, including viruses and bacteria. What Dr. Gendelman found was that macrophage cells actually carry HIV to the brain, where it causes dementia.

At first, the theory was discounted, but opinions changed after he co-authored a book on it — “The Neurology of AIDS,” now in its third edition — and found that similar observations linked macrophages to Alzheimer’s and Parkinson’s disease.

“There is a common mechanism,” he said. “What I learned from AIDS opened the door to the other neurodegenerative diseases.”

Based on his work, Dr. Gendelman just completed a proof-of-concept clinical investigation for a Parkinson’s immunization strategy that he soon hopes will enter Phase I testing.

Many people with AIDS suffer from brain damage and medication does not cross the blood-brain barrier. In a twist of science, Dr. Gendelman recently turned the macrophage from a disease carrier into a drug delivery system to get drugs across that barrier.

As part of his team’s nanoformulated antiretroviral therapy, or NanoART project, he has discovered how to use macrophages to carry ART directly to damaged and virus-infected disease sites. Nine senior scientists at UNMC are involved in the complex and multifaceted nanoformulations for this project.

“This could significantly improve the treatment of HIV/AIDS,” Dr. Gendelman said. With proof-of-concept in hand, the new therapy is anticipated to be tested in clinical trials within the next two years.

In the future, Dr. Gendelman hopes to address several problems associated with current HIV/AIDS therapy:

- HIV therapy is lifelong and complex. There are often many pills that need to be taken each day and for the rest of a patient’s life.
- While therapies prolong life, they also increase toxicity because of the length of treatment.
- Medications do not destroy the viral reservoirs in the body.
- Some patients who have HIV/AIDS — drug addicts, IV users and people in remote areas of Africa — experience the most difficulty with medication compliance.
Dr. Howard Fox, the Terry K. Watanabe Professor and medical director of UNMC’s HIV Clinic, showed that the transmission of HIV infection can be prevented in a relationship, if the HIV-infected person is given antiretroviral therapy;

Dr. Gendelman, professor and chairman of the department of pharmacology and experimental neuroscience and director of the Center for Neurodegenerative Disorders, leads a team that developed a new therapy that may allow patients with HIV to receive a weekly injection rather than take daily a regimen of pills to manage their disease. Called NanoART, it is funded by a three-year, $4.6 million grant from the NIH;

Dr. Fox, professor in the UNMC Department of Pharmacology and Experimental Neuroscience and senior associate dean of research and development for the College of Medicine, recently received a NIH center grant totaling $9 million to investigate the now chronic nature of HIV infection and its interaction with aging.

He directs the Chronic HIV infection and Aging in NeuroAIDS (CHAIN) Center and the Center for Integrative and Translational Neuroscience (CITN); and

Dr. Fletcher, dean of the College of Pharmacy, led a multi-center study that developed the first dosage guidelines for the protease inhibitor atazanavir in HIV-infected children as young as three months of age. In 1990, he also pioneered dosing guidelines for HIV-infected children that led to government approval of the drug efavirenz.

Dr. Howard Fox was a third-year medical student in a neurology clerkship at San Francisco General Hospital in the 1980s when he first saw HIV patients with neurological problems.

Later, as a scientist at the Scripps Research Institute in La Jolla, Calif., he studied HIV’s effect on the brain. Antiretroviral therapy helped reduce dementia, but Dr. Fox noticed that neurological disorders remained — patients couldn’t move or think easily.

By the mid-1990s, Dr. Fox began to hear about Dr. Gendelman and his work at UNMC.

“We worked in parallel worlds. I met him at meetings and now we work together along with Drs. Fletcher and Swindells in Omaha,” Dr. Fox said.

“We don’t know what the long-term effects of these drugs are or the long-term effects of the virus. There are 25,000 genes in the body, and we know little about how they interact. We need to look at everything — how gene expressions change in different states and how they work together.”

Dr. Fox’s NIH funded HIV Research Center will explore a field of biology that combines different techniques to identify, measure and correlate the broad range of proteins and molecules associated with neuroAIDS.

“As people with HIV/AIDS live longer on medication, they seem to age quicker and suffer from age-related conditions — atherosclerosis, cancers, heart disease and stroke. We see markers of chronic inflammation,” he said.

Macrophages, even when HIV infected, can live forever. HIV infection has become a chronic condition, like diabetes.”

With HIV growing in the over-50 age group, Dr. Fox said he wants primary care physicians to talk to their patients about safe sex.

“This was a generation that grew up worrying about getting pregnant. Now, it’s a generation that should be worried about getting HIV/AIDS,” he said.
Dr. Courtney Fletcher had just finished his doctoral program at the University Minnesota in 1982 when he became interested in viral infections.

His first NIH grant was to research HIV in children. After Communism fell in 1989, Dr. Fletcher was asked to help with an AIDS crisis in Ramania, where 94 percent of initial cases were in children under age 13.

“Sailors would donate blood in exchange for money in the Black Sea ports of Ramania,” he said. “Back then, the Romanian government believed that a daily microinfusion of whole blood would treat malnourishment and boost immunity for hospitalized and homeless children,” he said.

By the year 2000, 60 percent of Europe’s pediatric HIV/AIDS cases were registered in Romania; most were infants living in public institutions. For his work there, Dr. Fletcher was made an honorary member of the Romanian Infectious Disease Society.

By 1995, Dr. Fletcher’s work took him to South Africa, where he and colleagues treated children with anti-HIV drugs, in particular non-nucleoside reverse transcriptase inhibitors and protease inhibitors.

South Africa has the highest number of people infected with HIV in the world. In 2009, the United Nations estimated that 5.6 million people had HIV and AIDS in South Africa. In 2009, an estimated 330,000 children under age 15 lived with HIV, a figure that has almost doubled since 2001.

“I was surprised at the size of dosage needed to raise drug levels in children. They need much more than we thought — two to three times the dose per body weight,” Dr. Fletcher said.

“Children are not just small adults, their organs work differently in how they absorb and eliminate drugs.”

Before his arrival at UNMC in 2007, Dr. Fletcher was familiar with the work of Drs. Gendelman, Fox and Swindells. He now collaborates with all three on major studies, including a large international study on treatment strategies for HIV and tuberculosis.

Dr. Susan Swindells was treating HIV/AIDS patients in Columbus, Ohio, when she was recruited to UNMC in 1991 to help build an infectious diseases division.

Today, she is one of two physicians who serve 950 active HIV/AIDS patients in UNMC’s Specialty Care Clinic in Omaha. She is director of the Nebraska AIDS Education Training Center, principal investigator for many clinical trials and on the leadership of the NIH AIDS Clinical Trial Group.

An international expert in HIV, Dr. Swindells recently co-authored the world’s largest study to evaluate commonly used HIV drugs.

“At first, there was no treatment for HIV. Today, treatment is at the point where the disease is more a chronic, manageable condition, like diabetes,” she said.

She is concerned that HIV/AIDS causes rapid aging.

“We don’t know why that happens. Heart disease shows up 10 years earlier than it should in some people,” Dr. Swindells said.
Although Nebraska’s HIV/AIDS population is relatively small, Dr. Swindells still sees 10 new patients a month.

“What’s scary is that one-fourth of the people carrying the virus don’t know they have it and can easily pass it on. Globally, we’re losing the battle. The virus spreads due to war, famine, poverty, misconceptions, fear and ignorance. It’s a highly politicized disease and I’m worried that people have become complacent,” she said.

UNMC’s latest development in HIV treatment has combined three medications in a single pill taken once a day.

“I’m excited — a single injection would be a huge step forward in treatment,” Dr. Swindells said.

Many people are surprised that this important research is being done in Nebraska, she said.

“It works well for us. We get a lot of support at UNMC. We work well together, there’s less competition for everything and no backstabbing. It’s a productive atmosphere.”

April 26, 1987, is a day Eric Ernsberger wishes he could do over. That day, he shared a needle with someone who was HIV positive.

No longer addicted, Ernsberger, 49, has had a difficult road, but considers himself to be lucky to have survived and to have had UNMC’s help.

He was in San Francisco and had health insurance until his insurer cancelled coverage for every male who lived in his Zip code. Then he moved to Reno, Nev., where he had his first humiliating encounter with a health care provider.

“After I disclosed to the doctor that I was HIV-positive, he sent me back into the waiting room. Later, he stood across the crowded room from me and discussed my case in a loud voice in front of everyone,” he said.

An artist, he moved to Omaha to care for his elderly mother 16 years ago and met Dr. Swindells.

“She saved my life. I worship her,” he said. “UNMC is absolutely amazing. Everyone has gone out of their way for me.”

Treatment has improved dramatically since those early years, from AZT to the protease inhibitors. Ernsberger understands how critical it is to maintain a strict medication regimen.

“I’ve seen what happens when people don’t comply with a drug schedule,” he said. This year, he buried his partner who had a progressive form of neuro-AIDS that consumed more than 50 percent of his brain.

Ernsberger has personally dealt with stage four kidney failure, hepatitis C, shingles and Kaposi’s sarcoma, a rare cancer that was a harbinger of the AIDS epidemic. His goal is to outlive his 75-year-old mother.

He is so grateful for the care he’s received that he participates in as many clinical trials as he can. At one point, he was in five different studies at the same time. In a compliance trial, in which he had to take a pill every four hours, he was the only person out of 500 to comply 100 percent.

“I’m the best pill-taker ever,” Ernsberger said.

After battling the disease for so long, Ernsberger said he’s begun to feel the effects of old age.

“I feel like I’m 20 years older than I am. I’m full of aches and pains,” he said. “Many of my friends who have managed their disease well are now dying from age-related diseases.”

He longs for the day that people look for a cure instead of control.

“Right now, we all live waiting for the other shoe to drop,” he said.
Nancy Kamrath has tried lots of diet programs.

“I know them all. I’ve done them all.”

And, each time, she has success in losing weight — for a while.

Now, the rural Rising City woman hopes to shed the extra pounds for good as part of a unique UNMC College of Nursing research study specifically geared to rural women like her.

She’s hopeful the web-based intervention for weight loss and weight maintenance will help her meet her personal goals to lower her cholesterol, shed about 50 pounds and, most importantly, keep the weight off. “This is a new approach,” she said. “It’s a lifestyle change.”

Kamrath is a newbie in the study designed to help about 300 women work toward lifestyle changes at home via Internet access rather than in organized groups. Researchers will evaluate three interventions — an interactive web site, a peer-led discussion group and e-mail counseling — to determine which is the most effective with the least cost.
“WE WANT WOMEN TO ADOPT LIFESTYLES AND BEHAVIORS THAT PROMOTE THEIR HEALTH AND ENHANCE THEIR QUALITY OF LIFE AS THEY AGE.”

Carol Pullen, Ed.D.

The Internet-based results could benefit rural women who have limited options for weight loss guidance, said Carol Pullen, Ed.D., principal investigator on the $3.2 million Women Weigh-in for Wellness study, funded by the National Institutes of Health, National Institute of Nursing Research.

“Obesity is costly to the nation, as well as to people’s health,” she said.

An estimated two-thirds of Americans are overweight or obese and face a higher risk for diabetes, heart disease and possibly cancer.

“This study is well-suited for peri- and post-menopausal rural women who want to prevent disease and improve their health and function so they can maintain an independent lifestyle as they age,” said Dr. Pullen, professor in the Department of Community-Based Health in the UNMC College of Nursing. “Changes in diet and exercise to promote weight loss and prevent weight regain can significantly change the risk.”

Study participants — all between the ages of 45 and 69 who live within 50 miles of Columbus, Neb., and are overweight or obese — will post online their diet and activity levels, answer questions related to their behavior changes and receive online education and support for their goals. They also will make eight visits to the Central Community College — Columbus campus, which has provided facilities for the study, to receive initial and periodic health and fitness assessments.

Although the study lasts 30 months, Dr. Pullen hopes the healthy behaviors last a lifetime.

“We want women to adopt lifestyles and behaviors that promote their health and enhance their quality of life as they age,” she said. “In our earlier studies, about three-fourths of our women were overweight compared to two-thirds nationally.”

A native of Tennessee, Dr. Pullen worked on rural projects long before joining UNMC in the summer of 1993. Her interdisciplinary research has focused on health promotion of vulnerable at-risk rural women, specifically how to change their eating and activity levels to promote weight loss and lower blood pressure. She also works to reduce risk for cardiovascular disease.

Researchers have determined that weight loss programs delivered via the Internet may be an effective alternative to traditional programs for weight loss. But, Dr. Pullen said, there are few studies that examine weight maintenance.

Her research will be conducted in three phases: guided weight loss, guided weight maintenance and self-directed weight maintenance. Women who follow the plan should be able to lose up to 10 percent of their body weight in six months. Through healthier behaviors, they also are more likely to maintain their weight loss, as weight regain often occurs within one or two years.

“We tell the women in the study that it’s hard work. It’s a journey,” Dr. Pullen said.

“Increasing women’s physical activity to recommended levels is essential for preventing weight regain,” said Pat Hageman, Ph.D., professor of physical therapy education in UNMC’s School of Allied Health Professions and a member of the research team.

Kamrath — a busy mom to four, grandmother to 11 and cake shop owner — is up for the challenge.

“I’d like to see some weight loss every week, at least a pound,” she said. “Maintenance is the hard part, but, I know every diet program inside and out and this is an approach I can follow.”

For more information, contact Maureen Oberdorfer, project coordinator, at moberdorfer@unmc.edu or Dr. Pullen at chpullen@unmc.edu.
JIM EUDY, PH.D., LEFT, DIRECTS THE NEXT GENERATION DNA SEQUENCING CORE FACILITY WITH ALOK DHAR, PH.D., WHO IS THE LEAD TECHNOLOGIST RESPONSIBLE FOR THE WET-BENCH COMPONENTS AND DAILY OPERATIONS OF THE ILLUMINA GAIIX INSTRUMENT.
Voyage into the building blocks of life — adenine, guanine, cytosine and thymine — the nucleotide bases in a molecule of DNA. Here, within these DNA nucleotides, lie answers to the mysteries of life’s genetic diseases.

The mission of the Next Generation DNA Sequencing Core Facility (NGS) is to sequence large amounts of DNA quickly and inexpensively, said Director Jim Eudy, Ph.D. “It took $2.7 billion and a factory full of DNA analysis instruments 13 years to sequence the first human genome. With the latest NGS instrument, we can do it in 10 days for less than $10,000.”

The advent of Next Generation DNA sequencing allows whole genomes — from humans and other animals to plants and bacteria — to be analyzed in a matter of days instead of months or years. The technology will significantly accelerate UNMC research and discovery in cancer, inheritable diseases, infectious diseases and autism.

“We can measure which genes are actively expressed at any given time (transcriptomes) and study the genetics of inherited diseases,” Dr. Eudy said.

The core facility is funded by grants from the National Institutes of Health, the Nebraska Research Network in Functional Genomics NE-INBRE, Molecular Biology of Neurosensory Systems CoBRE and the Nebraska Research Initiative.

The core facility works closely with the Center for Bioinformatics and Systems Biology at UNMC. Affiliated with the center are Robert Boissy, Ph.D., assistant professor, internal medicine, and Adam Cornish. Dr. Boissy leads the bioinformatics team that processes the data generated by the sequencer and assists with experimental design and analysis.

This technology holds great promise for genome-wide genetic analysis that may influence the treatment of human diseases, development of prognostic biomarkers and the identification of cancer-generating mutations or viral drug-resistance, he said.

“This technology will further our understanding of genetics at a much more rapid pace than has been previously imagined,” Dr. Eudy said. “It’s an exciting time to be performing genomics research.”
Jennifer Larsen, M.D., wants to recruit more translational investigators who can transform discoveries from the laboratory into new treatments in the clinic and then into the community.

A translational research team includes multiple senior scientists with different types of expertise, she said.

One such team at UNMC has successfully attacked the problem of neuro-AIDS — when the virus changes brain function. The team found that inflammation was the cause and has reformulated medications to pass through the blood-brain barrier to target the source (see story page 5).

Another team looks at the important clinical problem of antibiotic resistant staphylococcal infections, or MRSA. They have found the reason why this infection is so hard to treat and have begun to develop new materials that may be more resistant to these types of infections.

“Multiple investigators with different skills and perspectives result in a speedier and more effective solution to a complex problem than one scientist could develop alone. This is translational science,” Dr. Larsen said.

“Changes in health care occur more rapidly when teams of basic, clinical and public health investigators of different backgrounds and research skills work together to tackle problems that lead to disease or health disparities,” she said.
“Discovery, by nature is bidirectional — sometimes we approach a problem from the basic science laboratory and bring it into the clinic or hospital.”

“Sometimes observations are made in the clinical setting that can be solved in the laboratory, which we call bedside-to-bench research,” Dr. Larsen said.

But translating a discovery into the community can be more challenging.

“For example, many studies have shown that weight loss prevents type 2 onset diabetes, but we have not been effective at persuading or achieving weight loss in many individuals at risk.”

Dr. Larsen is one of those translational research scientists, having done both basic and clinical research as well as working with Native American communities on public health initiatives to prevent diabetes.

“Our basic science research programs are strong and we will continue to focus on strategies to grow this area at UNMC,” Dr. Larsen said.

“However, if we can speed the translation of discoveries between the laboratory and clinical setting, and get them to the community, we could markedly improve the health of our communities and grow our research enterprise as well,” she said.

“At the same time, we need to further diversify our research portfolio. Prime examples of initiatives and resources that will support these new research directions are plans for a new Center for Drug Discovery and the development of the College of Public Health.”

Dr. Larsen, who was associate vice chancellor for clinical research, became UNMC’s vice chancellor for research on July 1 after Tom Rosenquist, Ph.D., stepped down. Dr. Rosenquist, who had led UNMC’s research enterprise since 1999, returned to the faculty in the department of genetics, cell biology and anatomy.

The principal investigator on four grants, including two from the National Institutes of Health (NIH), Dr. Larsen researches the metabolic consequences of organ transplantation and has conducted clinical trials with Native Americans to create strategies to prevent diabetes.

There are many strategies and tools to expand translational research. Already, UNMC investigators are using technology in their research, particularly to solve health issues in rural communities and decrease rural health disparities.

When technology helps bridge the distance into rural communities, it is called tele-research, Dr. Larsen said.

“UNMC investigators now use cell phones, websites and other mobile devices to monitor individuals participating in trials as well as to change behavior, or study devices that allow remote testing or consultation,” she said.

Technology also is used to inform health care providers in rural communities about clinical trials available to their patients.

Another growing area of research is the study of how genetics influence both the risk for disease as well as guide therapy. “Genetic tests now help us make treatment decisions so the right people get the right medicine,” Dr. Larsen said. This area of research is called pharmacogenomics.

Biomedical informatics — the application of computer science to biology and medicine — is essential to making these connections between genetic changes and health outcomes. This science also helps investigators understand and analyze images and other physiologic data, as well as trends in health using large public health data.

UNMC is working with sister campuses — the University of Nebraska at Omaha and University of Nebraska-Lincoln — to develop a collaborative graduate degree program in biomedical informatics to meet the need for specialists and investigators.
UNMC also is expanding its expertise in regenerative medicine — how to effectively create new cells when old or damaged cells or tissues fail — and comparative effectiveness research, which directly compares effective treatments for differences in outcome and cost.

UNMC’s research enterprise has grown dramatically over the past decade. Between 2000 and 2010 federal grants and contracts increased 234 percent from $27.3 million (adjusted for inflation) in 2000 to $91.6 million in 2010.

“Along with the growth in grants, our scientists have grown in stature as well. Our teams are internationally recognized for their breakthroughs in medical research,” she said.

UNMC researchers have made advancements in the fields of cancer, neuroscience, cardiovascular medicine, transplantation, nanomedicine, genetics, biotechnology, and infectious diseases, as well as rheumatoid arthritis, diseases of alcohol and smoking, rural health and health disparities.

“But, as our research enterprise expands and the NIH budget remains flat, we need to look for new research funding opportunities,” Dr. Larsen said.

Many UNMC investigators are exploring opportunities with the U.S. Department of Defense and the Agency for Healthcare Research and Quality.

Investigators have been linked with engineers and other industry partners to develop new biotechnologies that can create or attract industries in, and to, Nebraska.

“With increasing expertise in drug delivery and public health, we also have more opportunities to expand our research into the community.

“Increasingly, we target researchers in key areas to create broad translational teams. Our expanding research enterprise will rapidly improve the health of Nebraskans.”

**DR. BAYLES TAKES BASIC RESEARCH CHARGE**

The newest member of the research leadership team is Ken Bayles, Ph.D. He is the first associate vice chancellor for basic science research.

The position was created to facilitate communication about research programs and resources with the basic science research community and help the vice chancellor for research develop initiatives, programs and core facilities that will attract and retain scientists conducting cutting-edge science.

“Ken is an internationally recognized researcher who has built an accomplished translational research team,” said Jennifer Larsen, M.D., vice chancellor for research.

“He not only understands the importance of key technologies to basic science research but also understands the importance of basic and clinical investigators working together to successfully tackle our greatest health problems and grow UNMC’s research enterprise.”

Dr. Bayles, professor of pathology and microbiology and director of the UNMC Center for Staphylococcal Research, said he is invigorated by his new mission.

“One of my primary goals is to foster communication between our basic and clinical scientists,” he said. “Once the conversation starts, it doesn’t take long to find common ground. It is our mission to help develop this into a sustainable and productive collaboration.”

**DR. KRATOCHVIL WANTS TO GROW CLINICAL RESEARCH**

Since Chris Kratochvil, M.D., was appointed assistant vice chancellor for clinical research last year, he has started to unify and restructure the clinical research resources throughout campus and streamline the clinical research process for investigators.

“There are many different kinds of clinical trials. One of my roles is to match UNMC investigators with contract-related clinical research on campus. Already, this has led to greater research opportunities for our faculty and has benefited our patients,” he said.

Last year, UNMC was designated a prime site by Quintiles — the largest clinical research organization in the world — a development that stands to significantly increase the number of clinical trials conducted at the medical center, Dr. Kratochvil said.

Prime sites are large clinical institutions that collaborate with Quintiles to enhance their infrastructure for conducting clinical trials, improve efficiencies and increase productivity.

UNMC is one of just four Quintiles prime sites in the U.S.
Voices in the plaza work to improve research, health

The plaza — it’s the heart of any small town or village.

It’s a place where city services such as government, schools and health care are found and where people come together to celebrate, share information and socialize.

Based on that concept, UNMC faculty in the College of Public Health initiated the Plaza Partnership Project to bring more than 90 agencies in South Omaha together to collaborate on community-linked health research that will address such complex issues as childhood obesity, mental illness and prenatal care for undocumented women.

“If we are to discover breakthroughs in community health, it makes sense to bring people together in new ways to ask hard questions and find fresh solutions,” said Magda Peck, Sc.D., principal investigator of the three-year project that is funded by a $993,063 grant from the National Institutes of Health.

By building greater trust within the community and partnering with agencies already on the ground, we can conduct more meaningful health research, Dr. Peck said.

The four “plaza partners” in the project are UNMC, the South Omaha Community Care Council, Douglas County Health Department and OneWorld Community Health, Inc. Each group, in one way or another, already is engaged in the South Omaha community and has a vested interest in the success of future health research projects, she said.

A basic challenge is getting people who live and work in a community to understand the value of research.

“There is a degree of skepticism when researchers come into communities of color,” said Alberto Cervantes, president of the South Omaha Community Care Council, and one of three community research associates funded by the grant.

That skepticism is based on years of “helicopter” research when researchers would drop into communities, conduct their studies then leave just as abruptly. Unfortunately, people in such communities never experience the benefits of the research or see the outcomes, which leads to mistrust, Cervantes said.

What this project does, he said, is bring people together where they have a voice.

In the past six months, Cervantes and Christopher Fisher, Ph.D., assistant professor in the UNMC College of Public Health, have held forums and workshops with members from all four project partners, to discuss community-based health research, its benefits and how to get involved.

The groups also discussed strategies for engagement, related to research and data needed to improve the health and well-being of the South Omaha community. The conversations, the first of a series, will continue to be held among, and at, all four partner organizations and beyond for the duration of the project.

“It’s vital that we ask questions that are important and directly related to the community,” Dr. Fisher said.

Anne O’Keefe, M.D., senior epidemiologist with the Douglas County Health Department and another community research associate, agrees.

“My hope is if we can change how research is done, then people in the community will be more invested, the research will be more relevant to the people and we’ll have better outcomes,” Dr. O’Keefe said.

The leadership of the Plaza Partnership Project, which also includes Kris McVea, M.D., chief medical officer for OneWorld Community Health, Inc., and Shinobu Watanabe-Galloway, Ph.D., associate professor of public health, will collaborate with partners from across the plaza to develop timely and relevant reports on health data specific to South Omahans.

In January 2012, the project will launch the next phase to generate new and innovative research by and for South Omaha — the Research Action Learning Collaboratives.

Teams, led by a community member and a researcher, will engage in nine months of training to increase capacity, build skills and develop mutually beneficial research questions. The teams will emerge at the end of the process with the tools to obtain federal funding for their projects.

The bottom line, Dr. Peck said, is to generate great research together that can be translated into new ways that people and communities can become healthier.

Get involved in the Plaza Partnership — contact Dr. Fisher, cfisherm@unmc.edu.
Everywhere he goes, Wally Thoreson, Ph.D., can’t help but ponder the science behind what he sees. Even a stroll through the Amsterdam flower market in Holland starts him on a thought process about the regulation of synaptic release, cones and color perception.

Dr. Thoreson, a professor in the departments of ophthalmology and visual sciences, and pharmacology and experimental neuroscience at UNMC, has spent more than 25 years studying how sensory signals are transmitted from the eye to the brain to give meaning to the things we see and hear. His research, published in the August issue of Nature Neuroscience, could lay the necessary groundwork to develop new treatments for a variety of degenerative diseases of the eye and ear such as Usher’s syndrome and rod-cone dystrophy.

“An understanding of how these signals are transmitted can give us a better understanding of the causes of neurodegenerative diseases,” Dr. Thoreson said.

His research also has led to a better understanding of the role of synaptic ribbons, specialized structures found in sensory neurons that help transmit information.

The photoreceptor synapse is one focus of Dr. Thoreson’s research. This critical synapse transmits the information needed to determine what the eye sees, he said.

It does this by translating visual stimuli into electrical signals that are sent along sensory neurons into the brain via the synaptic ribbon. The synaptic ribbon releases information...
Fluorescent dyes light up a cross-section of a salamander retina to show a rod (white), cone (yellow), horizontal cell (magenta) and a bipolar cell (blue). The horizontal colored lines are the recording electrodes.

packaged in neurotransmitter-filled packets which carry it into the brain. These rapidly moving packets are in constant motion in order to keep up with the flow of new information.

“It’s amazing to think about the role of the synapse, the process by which it conducts information and how one small alteration to this process can change the way a person sees color,” he said.

“The way the world looks is a consequence of the way information is sent along those synapses. Diseases of the eye — night blindness, color blindness or rod cone dystrophy — involve damage to proteins used in that process,” Dr. Thoreson said.

By studying the photoreceptor synapse and the regulation of the release of these proteins along the synaptic ribbon under normal circumstances, Dr. Thoreson hopes to learn more about what happens when these proteins malfunction and lead to vision loss.

“I’m hoping my studies also will help us understand how this process works in other neurodegenerative diseases,” Dr. Thoreson said.

His research has given him an appreciation for the amazing capabilities of the human eye: the ability to see light at levels where only a few photons fall on the eye to light intensities 10 billion times greater, the diversity of colors perceived using only spectrally-distinct types of cones, and even how small disruptions can have a major impact on the function of the eye.

“I have always been fascinated with vision, how it is perceived and where that perception of what we see originates, in the eye or in the brain,” he said.

As a boy, Dr. Thoreson was particularly interested in insects and how they see and smell.

He studied insect pheromone receptors in graduate school with plans to develop a novel approach to help farmers control pesky bugs without the use of pesticides.

“Unfortunately, no one in entomology was qualified to teach the electrophysiological techniques I needed to conduct those studies, so I switched to vertebrate physiology and a different sensory receptor — the eye,” Dr. Thoreson said.

Twenty-eight years later, Dr. Thoreson still studies how photoreceptors in the eyes work by using salamanders, whose retinas are physiologically similar to humans.

He has received more than $5 million in research support from the National Institutes of Health, Research to Prevent Blindness and Fight for Sight.

“At the end of the day, it’s my hope that by understanding the basic function of vision, we are able to repair and restore sight,” Dr. Thoreson said.
Homing in on pancreatic cancer

With the deaths of Apple founder Steve Jobs and Nobel Prize winner Ralph Steinman, M.D., pancreatic cancer is back on the public’s radar screen.

But, for UNMC researchers — who recently landed a $4.2 million grant from the National Cancer Institute — it’s a constant quest to better understand, and halt, the deadly cancer.

“Our ultimate goal is to determine what makes pancreatic cancer so lethal,” said Surinder Batra, Ph.D., professor and chairman of the UNMC Department of Biochemistry and Molecular Biology and the principal investigator on the five-year grant. “We want to develop new therapeutics that work on pancreas cancer, because the drugs currently being used are not working.”

Pancreatic cancer is arguably one of the most lethal cancers. Annually, more than 44,000 Americans discover they have pancreatic cancer. More than 95 percent of those diagnosed die within a few years of diagnosis.

There are no screening tools for pancreatic cancer and the location of the pancreas, deep in the abdomen, hinders early diagnosis.

UNMC has established itself as a national leader in the study of pancreatic cancer with unique resources and more than $25 million in overall research funding through several NIH grants.

Dr. Batra’s team will study animal models and human pancreas tissue.

“We will look at the role of the tumor micro-environment of cancer cells,” Dr. Batra said. “We will try to figure out what makes these cells so aggressive, so resistant. We will study the pancreas, which is loaded with insulin, and try to determine if this environment is what makes pancreatic cancer so hostile.”

Three other UNMC investigators will serve as project leaders along with Dr. Batra. They are:

- Tony Hollingsworth, Ph.D., professor in the Eppley Cancer Institute;
- Rakesh Singh, Ph.D., professor of pathology and microbiology; and
- Keith Johnson, Ph.D., professor in the College of Dentistry.

Foundation grants support research collaboration in China, India

International research programs at UNMC focused on diabetes, environmental health factors and lymphoma have received support through $250,000 in grant awards from the University of Nebraska Foundation.

The grants support UNMC’s substantial international programs, said Chancellor Harold M. Maurer, M.D., and enable research teams to conduct pilot studies through collaboration with institutions and colleagues in China and India. The awards also prepare UNMC to apply to the National Institutes of Health for support of these studies.

UNMC faculty members who received the awards are:

- Nora Sarvetnick, Ph.D., director of the Nebraska Regenerative Medicine Project – $50,000 to support first-year research needed for a collaborative study of genetic and immunological features associated with Type 1 or insulin-dependent diabetes in India.
- Pinaki Panigrahi, M.D., Ph.D., director of UNMC’s Center for Global Health and Development in the College of Public Health – $100,000 to support research on the effects of environmental toxins on the health of mothers and infants in rural areas of India.
- Wing-Chung (John) Chan, M.D., the Amelia and Austin Vickery Professor of Pathology – $100,000 to support a collaborative lymphoma genetics research program between UNMC and the Chinese Academy of Sciences.

Eppley Institute celebrates 50 years of research

The Eppley Institute for Research in Cancer and Allied Diseases — or simply the Eppley Institute as it’s commonly called on campus — celebrated its 50th anniversary in September.

Founded with funds from the Eugene C. Eppley Foundation, National Institutes of Health and the University of Nebraska, the institute has for half a century been a place where researchers work to understand cancer and improve its diagnosis, treatment and prevention.

The institute was initially part of the College of Medicine but, in 1972, became an independent research institute that fell under the jurisdiction of the UNMC chancellor.

Today the institute employs 31 faculty members who conduct cutting-edge basic and translational cancer research.
**Dr. Kabanov receives ‘mega-grant’ from Russian government**

UNMC nanomedicine guru Alexander “Sasha” Kabanov, Ph.D., D.Sc., will operate labs on two continents thanks to a two-year, $4.5 million “mega-grant” from the Russian government.

Dr. Kabanov, the Parke-Davis Professor in Pharmaceutics and director of the Center for Drug Delivery and Nanomedicine at UNMC, is one of 40 Russian, foreign or expatriate Russian scientists who last year received a new type of grant to bring their expertise to Russian universities.

Dr. Kabanov joins an elite group of grant winners: One is a Nobel laureate and another holds a Fields Medal, commonly regarded as math’s Nobel Prize.

The only chemist in the group, Dr. Kabanov will lead one of six projects at Moscow State University (MSU), his alma mater. He will study chemical formulations of enzymes and proteins for bionanomaterials.

“I am looking for a different approach to therapy for drug-resistant bacteria,” he said.

The grant from Russia recognizes the quality of Dr. Kabanov’s research, said Don Leuenberger, vice chancellor of business and finance.

The 12-billion-rouble (U.S. $428 million) ‘mega-grant’ program is part of Russia’s attempt to strengthen research at its universities and modernize the country’s science and economy at large.

Dr. Kabanov’s laboratory will be in the MSU Department of Chemistry, where he also was a leading research fellow before the fall of the Soviet Union.

Dr. Kabanov and Leuenberger recently signed an agreement with MSU to protect intellectual property developed through this collaboration. The agreement, negotiated by UNeMed, UNMC’s technology transfer arm, also gives MSU the license to use Dr. Kabanov’s technologies that he developed at UNMC and gives UNMC access to enzyme engineering technology available at MSU.

**COPH lands two large grants with rural focus**

The two national grants total $7.6 million and fund two new regional centers to improve the health of rural Nebraskans.

The Central States Center for Agricultural Safety and Health — one of nine national centers funded by a five-year, $5 million grant from the National Institutes of Health — serves seven states and nearly one quarter of American farmers, said Risto Rautiainen, Ph.D., associate professor of environmental, agricultural and occupational health and administrator of the grant. The center will do research on asthma, agricultural injury surveillance and health and safety education of farmers.

During the past 10 years, agriculture has outpaced mining as the most hazardous industry in the nation, based on occupational fatality rates.

The Great Plains Public Health Training Center at UNMC is funded by a four-year, $2.6 million grant from the Health Resources and Services Administration. It is under the direction of Magda Peck, Sc.D., associate dean for community engagement and public health practice.

Since 2002, the number of health departments has grown significantly in Nebraska as has the need for expanded training of the public health workforce. The center will:

- Assess public health workforce needs throughout the state;
- Fund collaborative projects;
- Place students in the field; and
- Expand continuing professional education opportunities.
The study in the Sept. 26 online issue of the New England Journal of Medicine challenges a long-held belief that COPD always gets worse, never better.

“This is the first study to show definitively that COPD does not always get worse,” said Dr. Rennard, senior author of the paper and professor of pulmonary and critical care medicine in the UNMC Department of Internal Medicine. “This study establishes that the disease can be stable, at least over a three-year time frame, and may even improve some.”

Another key finding of the study revealed that patients with moderately severe COPD on average lose lung function more quickly than those with severe COPD.

“Drug development to slow the disease has been aimed primarily at those with severe disease when those with moderate disease are losing lung function faster,” Dr. Rennard said. “We’ve frequently ignored those with moderate COPD and not treated this stage of the disease aggressively. That may be a mistake.”

Study findings could change the focus of treatment for COPD to emphasize identifying those with COPD earlier, Dr. Rennard said.

Whether specific treatments can stabilize lung function or improve it will need to be studied, Dr. Rennard said.

“This will change the way we think about the disease and is a cause for cautious optimism,” Dr. Rennard said. “The key message is that it’s not hopelessly progressive in everyone.”

Watch Dr. Rennard explain how the research offers new hope to COPD patients.
Big things come in small packages

Tatiana Bronich, Ph.D., develops bullets that carry drugs to hit precise targets.

The targets — disease sites in the body that, up until now, have been hard to reach.

Dr. Bronich, associate director of the Center for Drug Delivery and Nanomedicine and professor of pharmaceutical sciences, directs the Nanomaterials Core at UNMC where the microscopic drug delivery systems are customized to treat stroke, hypertension, traumatic brain injury, obesity, Parkinson’s disease and cancer.

The Nanomaterials Core supports eight COBRE (Centers of Biomedical Research Excellence) project leaders in the development of nanoscale polymer materials — particles 100,000 times smaller than the head of a pin — for drug delivery, their characterization and safety evaluation.

Alexander Kabanov, Ph.D., D.Sc., received the $10.6 million COBRE in October 2008. The five-year grant is part of the National Institutes of Health’s Institutional Development Award (IDeA) program.

Dr. Kabanov, director of the Center for Drug Delivery and Nanomedicine and the COBRE Nebraska Center for Nanomedicine, has used these tiny polymeric particles to build a world-class nanomedicine center at UNMC to develop novel drug delivery systems.

Dr. Bronich and her team use state-of-the-art equipment to produce materials for biomedical research and develop new technologies not yet employed in research. Core researchers develop nanozymes as a platform technology for delivery of antioxidants and antiviral drugs to targeted sites.

Nanomaterials have a unique niche in the growing field of personalized medicine. “One system can simultaneously diagnose, treat and then follow the treatment using reporter molecules that show what’s going on in a noninvasive way,” Dr. Bronich said.

“Innovation is the exciting part of this job. We’re working with new materials that are responsive to external stimuli — magnetic field or optical signals — so we can purposely switch the drug system on and off. We can deliver a drug to a site in the body and have it wait there until we send a signal from outside.”

The external signal is like a key in an ignition — it won’t activate an engine (drug) until the key is turned.

“This could be an enormously useful tool for clinicians,” she said. “Once the drug is docked at the cell, then we can tell it when and how much to deliver. In many diseases, it’s critical that the drug is actively delivered to its target over a long period of time.

“Our goal for the Nanomaterials Core is to provide researchers a toolbox of resources that can be used by the entire UNMC community,” she said.
Primary care is the foundation for all health care in the United States. At the University of Nebraska Medical Center in Omaha, our novel approaches to primary care medicine are recognized nationally. The US News & World Report ranks UNMC’s primary care program seventh, among other prestigious universities. At UNMC, we believe that teamwork—among our physicians, physician assistants, nurses, nurse practitioners, pharmacists, public health workers and others—ensures that our patients receive the best and most innovative care possible. We continually explore new models of team care and how to best educate the next generation of health care professionals, ensuring a healthier future for patients in Nebraska and across the nation. UNMC. Breakthroughs for life.