UNMC’s research stretches around the world
UNMC’S GLOBAL PARTNERSHIPS

This issue of UNMC Discover focuses on UNMC’s global research partnerships. Some might ask, why do UNMC researchers work with partners outside the United States? In some cases, global partners come to us to collaborate. When an investigator is recognized nationally and internationally for their research, many people want to collaborate with them on research projects. Second, it is good for Nebraska’s economy. UNMC research is an important economic driver in Nebraska and “going global” with that research also is good for the Nebraska economy. Research spawns innovations, and some of those ideas lead to new products. These products, once licensed and developed, may improve health and be an economic boon to the state.

One such example is described in this issue. A new anti-inflammatory product called creatine ethyl ester, developed by UNMC investigator Jonathan Vennerstrom, Ph.D., in the College of Pharmacy, was licensed by Vireo, Inc., which built a manufacturing plant in Plattsmouth and created new jobs in Nebraska. But the story doesn’t end there. UNeMed, UNMC’s technology transfer office, helped introduce representatives of Vireo to a biotechnology company in China interested in importing and distributing the product in China. This agreement should bring new revenue, and even jobs, to the state. Finally, UNMC signed an agreement to pursue new research collaborations in China that further enhances the product.

A third reason our investigators work with global communities is because it provides access to unique populations needed to solve health problems. Some of those problems are more common outside the United States — such as malaria, tuberculosis or HIV. Stephen Obaro, M.D., Ph.D., described in this issue, is focused on combatting bacterial infections that are more common to children in Nigeria. Increasingly, we also are asked to help prevent problems familiar to us that are now increasing in other countries — obesity, heart disease, and diabetes.

The fourth and most common reason UNMC researchers work globally is that research is now global. We want the best collaborators on every research team. In some cases, those collaborators are located at UNMC or other University of Nebraska campuses, but they also may include researchers at other universities in the U.S. or halfway around the world.

Our students, whether international or not, assume they too will work on research as part of global research teams. In this issue, we will describe a unique grant that Amr Saliman, M.D., Ph.D., has focused on training students to conduct cancer research in global settings.

As you can see, we’re not isolated from global health issues just because we’re in the center of the U.S. In fact, sometimes our location helps us address those issues better. UNMC researchers are used to working across distances. Many of the same technologies and strategies we develop and use to conduct research and improve health across our large rural state are the very techniques that allow us to easily collaborate with researchers to address health concerns around the world.

Jennifer Larsen, M.D.
UNMC Vice Chancellor for Research
ON THE COVER:
UNMC’s research stretches around the world and strengthens global connections.

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UNMC’s research stretches around the world
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Collaboration provides a means for both professional advancement and increased knowledge. It offers access to resources and association with the scientific elite.

Today, research collaborations stretch around the world and connect the brightest minds in search of answers to complex problems. These collaborations enable scientists to share resources, equipment, specimens and expertise.

At UNMC, investigators partner with colleagues in such countries as Australia, China, India and Nigeria to advance knowledge in basic, translational and clinical research. Here, you’ll meet some of them and better understand why research collaborations strengthen knowledge, discovery and even the economy.

It would take 275 four-gigabyte hard drives, or 6,000 complete sets of the seven-book Harry Potter series, to hold all the data researcher John Chan, M.D., has generated from 22 lymphoma biopsies.

If this seems overwhelming, it is — even to Dr. Chan.

All this data comes from patients who had an indolent form of non-Hodgkin lymphoma (NHL) called follicular lymphoma and subsequently developed a more aggressive tumor called transformed follicular lymphoma.

Dr. Chan, the Amelia and Austin Vickery Professor of Pathology, has studied NHL for more than 20 years and has received more than $12 million from the National Institutes of Health and the Lymphoma Research Foundation.

In 2011, 66,360 people were diagnosed with NHL and 19,320 died from the disease in the United States. Transformed follicular lymphoma can be managed with chemotherapy and stem cell transplants, but patient survival was poor.

“About 40 percent of the patients experience transformation and once that happens, the prognosis gets much worse,” Dr. Chan said.

“We want to discover the genetic abnormalities associated with the transformation and find molecular targets for treatment.”

In follicular lymphoma, the bcl2 (B-cell lymphoma 2) gene that regulates cell death, or apoptosis, is moved, or translocated, to a new place on the DNA where its normal function is altered. It also is believed to be involved in resistance to conventional cancer treatment.

“Everyone has two sets of chromosomes,” he said. “It’s an accident of nature to get the first translocation of the bcl2 gene. This molecular change then allows subsequent additional genetic changes responsible for the development of the lymphoma.”

Although UNMC’s Next Generation Sequencing core laboratory enabled Dr. Chan to generate enormous amounts of sequencing data quickly, he needed greater capacity and assistance to analyze the vast amount of data. He turned to China.

For the past five years, China has poured trillions of dollars into biomedical research with the goal of becoming the global leader in life-science discovery and innovation. They have built five large capacity gene sequencing facilities, one of which is the Beijing Institute.
of Genomics (BIG) of the Chinese Academy of Sciences. With a computing capacity of more than 10 trillion calculations per second, BIG is focused on solving scientific questions through large-scale sequencing.

Enter Qiang Gong, a BIG graduate student and a bioinformatics expert, who was paired with WeiWei Zhang, a second-year bioinformatics graduate student in Dr. Chan’s lab. They worked for a while via email, but the 12-hour time difference and 10,628-mile distance hampered effective communication.

Dr. Chan used money from a University of Nebraska Foundation grant that had been set aside for global initiatives to bring Gong to Omaha for three months this past summer. The grant paid Gong’s travel and living expenses. When UNMC students travel to China, the opposite will be true, Dr. Chan said.

By September, Gong had worked with Zhang to establish a new, efficient algorithm to analyze data from Exome sequencing of the follicular lymphoma and the transformed samples.

“We can discuss data all the time and see if we can come up with new methods of analysis,” said Zhang, who had originally come from China to obtain her master’s degree at the University of Nebraska at Omaha. “Throughout this project, scientists and staff in UNMC’s bioinformatics facility have been engaged and helpful. The University of Nebraska-Lincoln supercomputer cluster, Tusker, has served as a workhorse for the analysis.”

Dr. Chan expects to complete the analysis by January 2013, after which they will publish their results and Gong will be honored as a co-author.

Graduate students Weiwei Zhang and Qiang Gong collaborate from half a world away on cancer research.

International collaboration moves research forward
by Kalani Simpson

We’ve heard much about why it is important for UNMC to establish collaborative relationships with China and others in the international science community. But what about the reverse? Why are China and Chinese scientists excited about collaborating with the United States and with UNMC?

Yong Zhao, M.D., Ph.D., is a professor of transplantation biology research at the Institute of Zoology, Chinese Academy of Sciences (CAS). He returned to China after serving four years as an assistant professor in surgery and the department of pharmacology and experimental neuroscience, where he retains his title and continues his research on a part-time basis.

In August he attended the eighth annual International Student Research Forum at UNMC — the second time the med center has been host - with 75 students from China, Australia, Japan and the U.S. He also attended the fourth annual Joint Research Symposium, which fosters collaboration among UNMC and Chinese investigators.

Dr. Zhao answered the question with an allegory - the chair he was sitting in. He said one person could probably move it by himself.

“But if we have to move a bigger chair,” he said, gesturing toward the loveseat to his left, “we might need two people. Or four people.

“You have to collaborate,” he said.

Science is full of big chairs.

Dr. Zhao collaborates with UNMC’s Jialin Zheng, M.D., professor of pharmacology and experimental neuroscience and assistant vice chancellor for academic affairs. They recently published a paper in the Journal of Immunology, “Transcription factor FOXO3a mediates apoptosis in HIV-1-infected macrophages.”

Dr. Zhao also is a UNMC/CAS liaison during trade missions between the two countries.

Dr. Zhao noted that he’s had a few of his students visit UNMC — some supported by the Chinese, some backed by principal investigators’ grants here.

Of those, one Ph.D. went back to China and became an associate professor. Two more are doing research as postdocs in the United States.
Science partnership opens opportunities between UNMC, China

In August, one of the most extensive partnerships ever between the United States and Chinese academic institutions was finalized between UNMC and Tongji University.

The agreement — called the Shanghai-U.S. Health Science Initiative — is a collaborative health science partnership that involves educational, clinical and research components. It was signed during Nebraska Gov. Dave Heineman’s trade mission.

“The partnership will pay tremendous dividends for generations to come,” said Gov. Heineman after a tour of Tongji University.

The partnership elevates UNMC’s stature in China, said UNMC Chancellor Harold M. Maurer, M.D. “This puts UNMC in an elite class among U.S. universities with a strong presence in China.”

The agreement will involve six different disciplines — medicine, physical therapy/rehabilitation, nursing, dentistry, public health and pharmacy — and will provide new opportunities for students and faculty.

Key elements of the initiative include:

- Development of a Research Collaborative Center that will focus primarily on research dealing with stem cells, nanomedicine, neuroscience and oncology;
- Development of a family medicine training program tailored to the needs of China;
- Hospital administration training through UNMC’s hospital partner, The Nebraska Medical Center;
- Up to 10 Chinese students annually will come to UNMC to seek doctoral degrees in medicine, physical therapy, pharmacy, nursing, dentistry and public health (or a master’s degree in public health) or do their medical residency training. Students will be financially supported by the China Scholarship Council;
- Health science students from UNMC will have the opportunity to be trained in China with educational experiences and clinical rotations coordinated through the initiative; and
- Development of a collaborative training program for American and Chinese students enrolled in Tongji Medical School. UNMC faculty members will help with the curriculum development and integration. Medical students would receive clinical training in the six affiliate hospitals of Tongji University.

This fall, two Chinese medical students were enrolled in UNMC’s College of Medicine, marking the first time the Chinese government has funded medical training in the U.S. for Chinese students, said Jialin Zheng, M.D., UNMC assistant vice chancellor for academic affairs and a key intermediary between the two universities.

New market in China = more jobs in Nebraska

A new market of 1.3 billion people opened this year to two nutritional supplements developed at UNMC.

AminoActiv, an anti-inflammatory cream or capsule, and CON-CRET, one of the bestselling muscle-building supplements in the United States, will now be distributed in China through a first-ever agreement signed between Vireo Resources and Beijing Ronghuaboshi Biotechnology Inc.

UNeMed, the technology transfer arm of UNMC, facilitated the agreement, said UNeMed President Michael Dixon, Ph.D. The agreement was signed during an August trade mission with Nebraska Gov. Dave Heineman.

In the three years since the company opened a manufacturing plant in Plattsmouth, Neb., sales have grown an average of 240 percent each year and the number of employees has increased to 12, with more jobs expected to be added next year. The plant was located south of Omaha because of the proximity of UNMC and its researchers.

Jonathan Vennerstrom, Ph.D., professor of pharmaceutical sciences, and Tom McDonald,
It’s 1 o’clock in the afternoon on the first Thursday in October and there’s a delivery for research technologist James Askew in the Durham Research Center II.

He opens the FedEx envelope carefully. Inside are 10 screw-top tubes full of saliva. The specimen samples traveled all the way from Perth, Australia, where children between the ages of 4 and 6, with identified language impairments, spit into them. When there’s a big enough batch of samples to mail — about every two to three weeks — a collaborating researcher sends them on a two-day excursion to Omaha.

When Askew receives the samples, he places them on the countertop for tomorrow’s workload. Friday is DNA extraction day.

In the coming months, the lab staff, at the direction of Shelley Smith, Ph.D., director of developmental neuroscience at UNMC’s Munroe-Meyer Institute, will begin genotyping the DNA samples to test for “candidate genes” of language problems, such as stuttering, apraxia and speech delays.

So far, Dr. Smith’s lab has collected around 2,000 samples from Australia. They are currently sitting in a minus 20 degree Celsius freezer waiting for a ride on the “Bead Express” — a machine that will reveal more insight into what genes are responsible for language disorders.

“We hope to identify several genes that contribute to language impairments,” Dr. Smith said. “Those genes are likely to be part of a molecular pathway for development, and knowing the pathway can help us understand why it happens.”

Dr. Smith has studied the genetics of speech, language and reading disabilities for many years, but the Australian study is definitely her largest sample for language disorders, and the longitudinal nature of the study means that the process of language development can be tracked. After a recent five-year funding renewal from the National Institutes of Health, the goal is to collect around 5,000 saliva samples.

“The results of this study also could target how language disorders are diagnosed,” Dr. Smith said. “And there are certainly early intervention implications as well.”

The grant is actually through Mabel Rice, Ph.D., at the University of Kansas, who has been a collaborator and friend of Dr. Smith’s for more than 10 years. Dr. Smith points out that without Dr. Rice, the international collaboration would not be possible. Dr. Rice is quick to return the favor.

“Shelley has the respect of her international peers for her studies on the genetics of reading and reading impairment,” she said. “When I became interested in genetics etiology, I contacted Shelley. She is one of the best in her line of research.”
When a child wakes with a raging fever, there’s a certain panic that charges through a parent’s heart. Yet, that panic gives way to relief as parents in the United States rush their child to the nearest hospital for efficient, reliable and relatively affordable health care. But should that child wake in a mud hut in Sub-Saharan Africa, the parent’s only resources might be a few herbs or antibiotics borrowed from a neighbor.

The reality of the situation is all too common in Nigeria, the homeland of pediatric infectious disease specialist, Stephen Obaro, M.D., Ph.D.

“Sixty-five percent of the children die,” he says softly.

“It doesn’t have to be that way.”

Every time he visits a developing country, he thinks about the skills he’s acquired in the United States and the resources that go to waste here. “I compare that to the lack of basic necessities needed to support the life of a critically ill child in poor countries. The inequity frustrates me.”

Now, he plans to change that.

In November 2011, Dr. Obaro received a $5 million grant from the Bill and Melinda Gates Foundation to provide the infrastructure and training, as well as the necessary data, to improve the clinical outcomes of critically ill children in Nigeria.

Through the grant, Dr. Obaro will establish better diagnostic services, provide microscopes and other equipment for basic lab work, and then train medical professionals at two teaching hospitals in north central and southwestern Nigeria on how to use the equipment.

The aim of the project is to identify the common causes of serious infections in children and to understand how underlying conditions, such as sickle cell disease, malnutrition and human immune deficiency virus (HIV) infection predispose children to life-threatening bacterial infections.

Recent studies from sub-Saharan Africa show that invasive bacterial disease, such as pneumonia, meningitis and sepsis — not malaria — is the leading cause of childhood mortality, Dr. Obaro said.

Too often, the lack of diagnostic equipment and trained professionals to pinpoint the cause of illness leads children with a fever to be misdiagnosed and treated with antimalarials or antibiotics.

What’s worse is that most government hospitals lack the necessary diagnostic facilities and equipment and must send samples to an independent lab where technicians may not be well trained.

“The amount of money the family has to pay for these services is weighed carefully by the doctor treating the child,” Dr. Obaro said. “Do they have enough to pay for both laboratory services and medication?”

In the U.S., it’s unthinkable to treat an illness without knowing the cause, but that’s the reality in Nigeria, Dr. Obaro said.

And while there are vaccines to prevent illness such as pneumonia and meningitis, they are not always the right ones, he said.

Pneumonia is caused by several types of viruses and bacteria. A particular type of bacteria, pneumococcus, is thought to be the leading cause of bacterial pneumonia in children worldwide. However, there are more than 90 different strains of these bacteria alone and understanding the prevalent strains in specific regions is key to formulating the appropriate type of pneumococcal vaccine.

“The best vaccine we have only contains 13 bacteria and it’s based on patterns of infection in the U.S., which doesn’t necessarily work in Nigeria or other countries,” Dr. Obaro said.

With proper diagnostic tools and training, researchers and health professionals can begin to understand what bacteria and viruses cause infectious diseases in Nigerian children and determine what vaccines are effective or look for new ones, he said.

“If we can harness our resources globally then we can truly make a difference and save lives.”

As part of a community survey for sickle cell disease, Stephen Obaro, M.D., Ph.D., takes blood samples from children living in Gwantu, Nigeria, during a visit last year. Sickle cell disease is a common, inherited blood disorder that increases susceptibility to certain types of serious bacterial infections.
UNMC’s public health students will learn how to conduct cancer research in underserved populations around the country and the world in a unique program starting next year.

Recruitment for the Cancer Epidemiology of Education in Specific Populations program is now under way and classes will begin in January. The program comes to UNMC with the newly appointed interim chairman and associate professor of epidemiology Amr Soliman, M.D., Ph.D.

Funded by a $1.2 million grant from the National Cancer Institute (NCI), the two-year program was transferred in September from the University of Michigan School of Public Health, Ann Arbor — one of the leading schools of public health in the United States.

It is the first training grant from the NCI to the UNMC College of Public Health, said Dean Ayman El-Mohandes, M.D., M.B.B.Ch., M.P.H. “This program is one of a few in the world that trains public health students in cancer research in special populations domestically and globally,” he said. “This is a tremendous plus for UNMC.”

Before Dr. Soliman was recruited to UNMC this year, he was an associate professor of epidemiology at Michigan, where he founded the program in 2006 and was its director. The grant was renewed last year for five years.

It started when he saw a need for qualified researchers in this field.

“Most international researchers fail because they don’t have the education, experience and the cultural sensitivity necessary to conduct studies in foreign countries. It’s necessary for all aspects — from questionnaire design to intervention development,” Dr. Soliman said.

During the first year, students take classes and work with a mentor in a four-month summer field internship. In the second year, students analyze the collected data, write and publish papers and present findings.

Studies focus on the collection of raw data — cancer incidence, environmental and occupational exposures, types of vaccines available, barriers to screening, outcomes to survival and cancer survival and control.

Students select from seven domestic and 13 international research sites, mostly in Africa and the Middle East, on how to conduct research and design prevention and screening methods in a culturally sensitive manner.

Students will be based at universities or with the country’s ministry of health.

While inflammatory breast cancer is rare in the United States, it is common in the North African countries of Morocco, Egypt and Tunisia, where the survival rate is poor, Dr. Soliman said. Colorectal cancer and lymphomas are common in the Sub-Saharan countries of Ghana, Kenya, Tanzania, Uganda and Malawi.

In the six years of the program, 62 students have graduated; 55 percent of them are employed in the field. “Some work for the NCI, some are faculty and some do research in the jungles of Africa,” Dr. Soliman said.

Each year, eight master’s of public health and two doctorate students will be accepted into the program. They will receive a stipend that pays for travel and living expenses at the research site and travel to conferences.

“It’s not easy to recruit public health students into cancer research,” Dr. Soliman said. “Most students don’t know about it.”
Nanomedicine may help prolong life of artificial joints

To Dong Wang, Ph.D., drug delivery is like adding salt to your food. You’ve got to get it right.

Now, with nanomedicine, we have the ability to target precise areas with precise doses. And during his postdoc training, Dr. Wang got the idea that nanomedicine might be used to target inflammation too.

Since UNMC is recognized for its work in nanomedicine, Dr. Wang, associate professor of pharmaceutical sciences in the College of Pharmacy, was onto something. And collaboration with orthopaedics gave him another idea.

Orthopaedic surgeons often see patients who suffer from difficulty brought on by tiny particles from the wear and tear of artificial joints.

“An inflammatory response to those particles leads to bone destruction, and that can cause big problems,” said Ed Fehringer, M.D., an adjunct associate professor at UNMC. Dr. Wang first collaborated with Dr. Fehringer, a former associate professor of orthopaedics at UNMC who went into private practice in 2012. The two have since broadened their interdisciplinary collaboration to include materials expert Hani Haider, Ph.D., professor, and surgeon Curtis Hartman, M.D., assistant professor in the department of orthopaedic surgery and rehabilitation. The department chairman, Kevin Garvin, M.D., also has been extremely supportive with clinical guidance and acquisition of major equipment, Dr. Wang said.

Enter yet another collaborator — Steven Goldring, M.D., chief scientific officer at the Hospital for Special Surgery in New York, the nation’s No. 1 orthopedics hospital according to U.S. News and World Report. Dr. Wang’s friend and mentor, he liked where they were going and offered the use of his mouse model.

Dr. Wang’s team injected the mice with particles and measured how inflammation attacked the bone. Later, they created another mouse model in which they inserted tiny titanium pins to simulate the effects of artificial joints in humans. Using an imaging probe based on their nanomedicine platform, the team searched for signs of inflammation before bone breakdown.

Imaging is possible because local blood vessels become leaky in response to inflammation. Normally that’s absorbed by the body and we’d never know it. But, by using the nanomedicine platform to target minute doses of radiation to the area, those leaks — the first signs of inflammation — show up on imaging scans.

In home-repair parlance, it’s like using soapy water to find an air leak in a tire. The resulting bubbles pinpoint escaping air, even from a hole too small to see.

“We want to see the implant failure coming,” Dr. Wang said. “We don’t want to wait until patients start to feel the pain in their hip or can hear a sound in their knee.”

The goal is to implement an early warning system. Caught early, inflammation in patients with artificial joints can be treated before it becomes a real problem.

And the team did see it. Using technology patented by Drs. Wang, Fehringer and Goldring, the investigators could see a difference in the leg with the particles before any bone erosion even appeared on a CT scan. “In other words,” Dr. Wang said, “we saw the initiating pathology before the real bone damage happens. That’s a big thing.”
The next step would be to preemptively treat the inflammation. Targeted anti-inflammatory nanomedicine would put the right dose in the right place, while minimizing the risk of side effects. And in the mouse models, that worked too: a study by one of Dr. Wang’s students showed the bone next to the implant was preserved.

The hope is to someday take that diagnosis and treatment technology and apply it to people — the kind of patients UNMC ortho clinicians see in their practice.

It would be better to have screening tests once a year, Dr. Wang said, than to wait six years or so, only to undergo another surgery, take out an old artificial joint, put in a new one, and start recovery all over again. 🚸
The UNMC/UNL viral immunology collaborative team at work in Dr. Petro’s lab at the UNMC College of Dentistry. From left, Ph.D. student Tyler Moore; Tom Petro, Ph.D.; Deb Brown, Ph.D.; and research technician Elizabeth Cody.
Each human is chronically infected with up to 10 viruses at some time in life.

Two of the most common: the Epstein-Barr virus, which causes mononucleosis, and the recently discovered Saffold virus, which causes early childhood infection.

Tom Petro, Ph.D., wanted to learn more about the mechanism of these chronic infections.

To do so, the professor of microbiology and immunology at the College of Dentistry began to investigate the role played by the interferon regulatory factor 3 (IRF3) gene, which is expressed in macrophages, the immune system’s first line of defense to viral infection.

He used two mouse models — one that is naturally susceptible to macrophage infection by Theiler’s Murine Encephalomyelitis Virus (TMEV), which is related to Saffold and can cause chronic inflammation in the brain, a condition that closely resembles multiple sclerosis in humans. The other model is resistant to chronic infection of the virus.

He infected them both with TMEV and found that the IRF3 response was dysfunctional in the mouse susceptible to infection and found the genetic basis for the difference in IRF3 behavior. “I believe this contributes to its natural susceptibility to TMEV,” Dr. Petro said.

By now Dr. Petro was in collaboration with Deb Brown, Ph.D., assistant professor at the School of Biological Sciences at the University of Nebraska-Lincoln and a viral immunologist at the Nebraska Center for Virology. Dr. Brown’s reviewers on grants and papers wanted to see if her findings with the influenza virus also were valid for other viruses — like TMEV.

“The collaboration made sense,” Dr. Petro said. “There are so few immunologists at UNL, and at UNMC for that matter, that collaboration is a necessity.”

They received a seed grant from the Nebraska Center for Virology to foster collaboration science. The team has two joint publications and is at work on a third manuscript.

Together, their work may give insight into the cause of chronic viral infection and perhaps even multiple sclerosis in humans.
It’s 10 a.m. at Brown County Hospital in Ainsworth, Neb., and time for medication.

As the nurse stands at the medication cabinet getting the meds ready, a lab tech approaches with test results. When she walks down the hall toward the patient’s room, a doctor approaches with some instructions and just before she enters the room a nursing assistant stops her to ask a question.

“What should only take five minutes turns into a 20-minute task,” said Tammy Brown, a registered nurse and director of nursing at the hospital.

With each interruption the chance for errors increases, Brown said.

Gary Cochran, Pharm.D., assistant professor of pharmacy practice in the UNMC College of Pharmacy, wants to help rural hospitals decrease the chance for errors.

Through a five-year, $650,000 training grant from the Agency for Healthcare Research and Quality, Dr. Cochran has completed one study and is launching a second comparing the effectiveness of medication use systems in reducing errors in a sampling of the 65 critical access hospitals in rural Nebraska.

The purpose of the grant is to help researchers learn new methodologies through hands-on experience, formal training and oversight by senior investigators.

Dr. Cochran used a unique practice-based evidence study design and new analytic techniques to better address the limitations of observational study designs.

In the next study, data collection forms will be developed entirely by the participants, allowing them to identify relevant questions, Dr. Cochran said.

“We will provide assistance with design, data collection and analysis,” he said.

The goal of both studies is to compare the different systems — bar coding, tele-pharmacy or a full-time pharmacist — that dispense medication.
medication to patients and the impact they have on reducing errors.

“More than 400,000 harmful medication errors occur each year in the United States,” Dr. Cochran said. “While significant advances have been made in large hospitals, little research has been conducted in the 1,300 critical access hospitals across the nation, where differences in personnel, infrastructure and care delivery processes make it hard to generalize findings from large urban facilities.”

In his first study of nine rural hospitals, including Brown County Hospital, Dr. Cochran evaluated more than 3,000 medication passes by nursing staff through direct observation by peers.

The technique allowed the participating facilities to discover their own strengths and weaknesses when it came to patient care, Brown said.

The impact from the first study already is evident at Brown County Hospital, where the findings helped hospital administrators implement technology to support clinical staff throughout the medication process, she said.

Those implementations included the purchase of an automated medication dispensing machine, as well as the addition of a licensed practical nurse and pharmacy technician who both work full-time in the pharmacy.

“And we’re looking into getting medication dispensing carts for the nursing staff,” Brown said.

Five of the nine hospitals that participated in the first research study are signed on for the next one, which will begin by May 2013.

“We want to see if the changes we’ve made have had an impact and if there are other areas of weakness that need attention,” Brown said.

That’s good news for Dr. Cochran, who is pleased his research is useful to the hospitals.

“Our hope is to improve medication safety, reduce harmful medication errors and improve the quality and efficiency of health care for those living in and traveling through rural America,” he said.
**PREGNANCY HORMONE MAY SAVE LIVES, LIMBS**

When diabetes claims a hand, finger, leg or toe, researcher Robert Bennett, Ph.D., knows it doesn’t have to be that way.

As associate professor of diabetes, endocrinology and metabolism at UNMC and a research chemist at the Omaha VA Medical Center, Dr. Bennett wants to help clinicians save lives and limbs.

He hopes relaxin, a naturally occurring hormone that helps prepare a woman’s body for pregnancy, holds the key to new therapies for liver, kidney and diabetes-related vascular problems.

Relaxin, which allows a woman’s body to stretch, and, in men enhances activity of sperm, has been shown to prevent and reduce fibrogenesis, or scarring on wounds and organs.

A member of the insulin family of hormones, relaxin works to keep collagen, a connective tissue protein that covers and protects wounds, from accumulating. Relaxin also relaxes blood vessels to reduce stress on the heart and kidneys and enhances the growth of new blood vessels.

Diabetes causes blood vessels of the foot and leg to narrow and harden. Poor circulation can make it difficult for extremities to fight infection and heal. More than 60 percent of nontraumatic lower-limb amputations occur in people with diabetes.

How relaxin helps blood vessels improve circulation is the focus of Dr. Bennett’s research into the beneficial effects of this polypeptide hormone. One of only 125 people in the world to study relaxin’s role on tissues, Dr. Bennett has exhaustively studied how it affects the liver.

Constant injury to the liver by alcohol, hepatitis and excessive use of acetaminophen cause the organ to produce an excess of collagen, which builds, hardens and turns into fibrosis and later cirrhosis of the liver. Every year, liver fibrosis and cirrhosis affects 900,000 people and causes 36,000 deaths in the United States.

Progressive scarring by fibrosis is a leading cause of organ failure worldwide. It causes loss of organ function when normal tissue is replaced with excess connective tissue. No therapy has been effective in fibrotic disease, which is considered an irreversible process and is still treated by anti-inflammatory and immunosuppressive drugs.

Scientists have found that relaxin clears scars by decreasing the amount of collagen, which allows liver function to improve so it can repair itself. Relaxin’s effects on the circulation also contribute to its antifibrotic actions. It’s been so effective against scarring that it is now in clinical trials for liver and kidney disease, lung fibrosis, acute heart failure and preeclampsia.

Although the relaxin gene has been identified, Dr. Bennett wants to pinpoint which cells actually produce the hormone. “My goal is to develop a technique that allows me to switch production on and off at will.”

He works with a mouse model in which the relaxin receptor does not work. So, while the hormone is produced, it cannot be activated anywhere in the body.

“I want to see what happens when relaxin is unable to do its job,” Dr. Bennett said.

He has studied the role of the relaxin receptor in hepatic stellate cells, the major cell involved in liver fibrosis. When the stellate cell is activated, it secretes collagen and factors that contribute to vasoconstriction which can lead to cirrhosis.

“After the mice developed fibrosis, I gave them relaxin and found that it cleared the scar and allowed the liver to repair itself,” he said.

Dr. Bennett is excited that a new mouse model that does not have the relaxin gene has been developed at the Knockout Mouse Project Consortium in California. Once he obtains some of these mice, he may be able to engineer a mouse model tailored more closely to his research.

With the risk for stroke two- to four-times higher among people with diabetes, the implications of this research to vascular-related diseases — heart disease, stroke and high blood pressure — are profound, he said.

“Relaxin has emerged as a natural suppressor of age-related fibrosis in many tissues, which include the skin, lung, kidney and heart. New targets and mechanisms for relaxin’s actions will provide unprecedented advances in the field.”

But for now, Dr. Bennett would be satisfied if his work helps to save at least one of the nearly 66,000 limbs claimed by diabetes every year.
Tammy Kielian, Ph.D., turned to the computer in her office and pulled up a picture of childhood joy: a young girl with glasses, with a sunbeam of a smile, the kind that reaches into your chest. “This is Olivia,” Dr. Kielian said.

Dr. Kielian, a professor of pathology and microbiology in the College of Medicine, beamed a little herself. “She’s a pistol,” Dr. Kielian said, then stopped, and looked at the picture again.

This is why she works now. This is why she does what she does. Olivia, the go-getter, the girl with the indefatigable smile, is Dr. Kielian’s 9-year-old niece; her sister’s youngest kid.

A while ago they noticed Olivia’s vision was getting worse. She went through two pairs of glasses before her family could blink. A second-opinion suggested it might be the first sign of something else, and it was. Genetic testing confirmed Olivia has juvenile neuronal ceroid lipofuscinosis, better known as Juvenile Batten disease. It’s inherited, autosomal recessive, neurodegenerative. That was a little over a year ago.

A bright smile drives genetic research

by Kalani Simpson

TAMMY KIELIAN, PH.D., HOPES THAT HER RESEARCH WILL HELP CHILDREN LIKE HER NIECE, OLIVIA, WHO HAS JUVENILE BATTEN DISEASE.
Juvenile Batten occurs in about one in 100,000 live births, Dr. Kielian said. That’s very rare — but it still adds up to plenty of kids. That’s a lot of families that will mark time in two ways — from the day before they heard the diagnosis and the day after.

“It changes everything,” Dr. Kielian said. Look at that picture again.

Basically: Mutation of the gene CLN3 results in lysosomal storage problems. An abnormal amount of protein and lipids become trapped inside the cells. Like when the garbage disposal breaks, the body can’t clean the clog.

As the material accumulates in brain cells, neurons in the central nervous system begin to die. The first symptom is loss of vision. Then seizures. Then cognitive loss, then motor loss. Then premature death.

A lot of kids who have it are gone by their late teens.

For the past dozen years or so, Dr. Kielian’s lab has investigated immune responses in the brain. She had an idea that maybe this had something to do with it; maybe her research might have an impact. She had to try.

David Pearce, Ph.D., an expert in the field, has published 60 papers on Batten. Dr. Kielian emailed the director of the Sanford Children’s Health Research Center in Sioux Falls, S.D., and proposed a collaboration. Almost immediately, her computer dinged with his reply. Then her phone rang, too.

Soon, Dr. Pearce’s mouse models — mice with mutated CLN3 genes, just like in these kids — were headed to UNMC.

And in these mice, Dr. Kielian found that the two types of brain cells she studies — the microglia, the brain’s first line of defense, and the astrocyte, which supports neuron viability — are activating early. Very early.

“We believe that when these cells turn on early, they inadvertently contribute to an environment that, down the road, leads to neuron death,” Dr. Kielian said.

Scientists see it all the time: sometimes our antibodies work against us.

“An overactive immune system may be contributing to this disease’s pathogenicity,” Dr. Pearce said.

Now, one of the goals in the study of Juvenile Batten is to slow down this process to give these kids more years and better ones.

Dr. Kielian hopes — along with investigators grateful for the fresh perspective — that her work will inspire other researchers.

Meanwhile, Olivia is doing it all with abandon. She’s in gymnastics and Girl Scouts. She’s learning braille. Her mom has her in everything, has her breathing life in with great gasping gulps.

Like Olivia ever had a problem with that.

Kids who have Juvenile Batten disease can sometimes rage against the dying of the light or they can seem detached.

This awful thing steals them, neuron by neuron. Sometimes parents don’t even tell their kids they have it. Sometimes that’s for the best.

Olivia understands that someday she may not see. Right now, that’s what she knows.

Dr. Kielian asked her sister and her husband if there was anything they didn’t want her to talk about for this story. No, they said. Say everything.

“Seizures will initially be controlled by medication,” Dr. Kielian said. “Eventually they won’t.”

Now, a catch in her voice: “Cognitive loss will occur.”

Dr. Kielian soldiered on: “Speech will go. She won’t really be able to communicate anymore. She’ll be in a wheelchair. After that, bedridden. And then the end.”

Silence.

One second. Two …

“Strangely enough, it doesn’t seem real right now,” Dr. Kielian said.

No, of course it doesn’t. Right now, she’s doing something. Right now, she’s getting funding, and readying proposals for more. Right now, she’s making presentations at national conferences and investigators are praising her new ideas. Right now, her sister is seeing this — her sister is going to conferences, too, meeting the scientists who are so hard at work.

Right now, their fight has only just begun.

But this is different. This isn’t in theory. This isn’t your typical investigation. This isn’t abstract.

They are on the clock.

She nodded at the assessment, repeated it with a whisper:

“We’re on the clock.”

But science doesn’t work like that. Research moves at its own pace; and Dr. Kielian has to detach herself — as a professional and a scientist. Her lab knows this story, of course. And she might mention her niece in an opening sentence at a conference. But, there is no picture of Olivia and her sunbeam smile in the lab or at presentations. There is no impassioned plea. There can’t be.

Research doesn’t work like that.

Instead, all she can do is push her sadness into a box and use it as fuel. And she does. And she will. This is what she’ll work on forever.

“And I will always do it for her,” she said. Always, for that go-getter girl with the smile you can feel in your chest.

“Always,” Dr. Kielian said. “That will never change.”
UNMC receives grants for equipment used in research, medical therapies

The University of Nebraska Medical Center has received two grants totaling nearly $142,000 from the University of Nebraska Foundation for new equipment used in research and medical therapies.

“The funding we received for new equipment proposals will help advance 21st-century biomedical research,” said Jennifer Larsen, M.D., vice chancellor for research. “Science continues to evolve. As a result, new equipment is essential to allow our funded researchers to continue to compete at a national level for new research funding as well as advance all types of research.”

The following grants were received:

- $112,337 to acquire a next-generation DNA sequencing device and its associated laboratory information management system. It enables researchers to conduct genome sequencing twice as fast at half the price while keeping the highly private data secure. Able to sequence human DNA in 24 hours, the information gathered leads to better medical therapies tailored specifically for an individual.

- $29,600 to acquire a new device able to rupture cells more gently, causing less damage to cell contents and resulting in more information gathered with better quality. This study of cell contents is the first step in many types of research, including cancer, drug discovery and development, normal cell processes, metabolic disorders, and more.

NU-DOD partnership brings opportunities for UNMC researchers

The University of Nebraska has entered into a long-term partnership with the United States Strategic Command (USSTRATCOM) at Offutt Air Force Base to create a University-Affiliated Research Center (UARC).

The center will serve as a primary research and development center that supports USSTRATCOM’s missions to deter and detect strategic attacks against the United States and its allies, and to defend the nation as directed.

Through the UARC — housed in the university’s National Strategic Research Institute, which the Board of Regents approved in May — NU will provide research and development services for USSTRATCOM in areas such as:

- Nuclear detection and forensics;
- Detection of chemical and biological weapons;
- Passive defense against weapons of mass destruction;
- Consequence management; and
- Space, cyber and telecommunications law.

“The UARC is a tremendous distinction for the University of Nebraska, which recognizes the outstanding capabilities of our faculty,” NU President James B. Milliken said. “This new UARC and the research it supports will be good for the university, the state and our nation.”

The UARC is a university-wide initiative that draws on a broad range of expertise from all four NU campuses. Faculty will have the opportunity to participate if their research aligns with federal funding opportunities.

The initial contract award from the Department of Defense to the university provides for up to $84 million over the next five years to support the early research activities of the National Strategic Research Institute.

UNMC researchers stand to make significant contributions in several of the UARC focus areas, said Jennifer Larsen, M.D., vice chancellor for research.

“Our investigators have the expertise that STRATCOM and other defense agencies need and want,” Dr. Larsen said. “By forming this new collaboration, we hope to provide benefits for the defense of our troops as well as new funding opportunities for our investigators.”

Only 14 U.S. institutions, including the University of Nebraska, host UARCs. Other institutions that host UARCs include the Massachusetts Institute of Technology and Johns Hopkins University.

A
d
powerful new drug to treat malaria — the
invention of a College of Pharmacy researcher
— will help take the bite out of malaria. In the United
States, a mosquito bite seems harmless, but in
developing countries it means more than 655,000
deaths a year — mostly in children.

The new drug, Synriam, is considered a
breakthrough, as traditional drugs are proving
increasingly ineffective against the deadly malarial
parasite because of acquired resistance to available
drugs. Taken as a tablet once a day for three days, it’s
more effective, cheaper, has fewer side effects and
does not have to be taken with food.

From 2000 to
2010, Jonathan
Vennerstrom, Ph.D., a
professor at the UNMC
College of Pharmacy,
led an international
team that created the
drug compound that
led to the development
of Synriam. Developed
by Ranbaxy Pharmaceuticals Limited, the medication
is approved for treatment in adults in India. The
company also is working to create a children’s
formula and make the drug available in Africa, Asia
and South America.

Dr. Vennerstrom and his team received more
than $12 million in grants from Medicines for Malaria
Venture (MMV), a non-profit organization in Geneva,
Switzerland. The research team included scientists
at the Swiss Tropical and Public Health Institute in
Switzerland and Monash University in Australia.
MMV receives about 60 percent of its funding from
the Bill and Melinda Gates Foundation.

“With more than 200 million cases of malaria
each year, the potential impact this drug could
have on saving and improving lives worldwide is
significant,” Dr. Vennerstrom said.

Two inventors were honored in October at
the 2012 Innovation Awards Ceremony,
sponsored by UNeMed, UNMC’s technology
transfer company.

Tammy Kielian, Ph.D., professor in the
department of
pathology and
microbiology, was
honored with the
Emerging Inventor
Award, along with
a research grant
of $25,000.

Dr. Kielian’s
research interests
span the fields of
neuroimmunology, infectious
diseases and neuroscience with a
unifying
theme of innate immunity. Her work focuses on
two major areas of research:

Investigating ways to prevent and treat
methicillin-resistant Staphylococcus aureus
(MRSA) infections by enhancing immune
responses. She recently filed a patent
through UNeMed to support technology
to utilize a patient’s own immune cells to
prevent and/or treat infections associated
with foreign devices, such as artificial hips
and knees.

Elucidating inflammatory pathways that
contribute to the death of neurons in the
brain during Juvenile Batten Disease. Her
lab explores the therapeutic potential of
various compounds to delay neuronal loss
and premature death in children suffering
from this disease. See
story page 18.

Greg Oakley, Ph.D., a
cancer researcher at the
UNMC College of Dentistry,
received the Most Promising
NIN (New Invention
Notification) Award from
UNeMed, along with a
research grant of $10,000.

Dr. Oakley’s research is in the area of DNA
damage and repair. Work performed in his lab
focuses on deciphering the associated signal
transduction pathways and how alternations
to these pathways can lead to mutations and
ultimately the beginning of cancer.
Study raises questions on sepsis drug taken off market

A study conducted by UNMC infectious disease specialist Andre Kalil, M.D., makes a case for a potentially life-saving sepsis drug that was taken off the market last year by the drug company that produced it.

Dr. Kalil, associate professor in the department of internal medicine, studied a non-antibiotic drug known as Xigris, which was taken off the market by its maker, Eli Lilly, in 2011 over concerns of its efficacy. Sepsis is a deadly blood infection that results in death in one-third of patients.

In his study, published in the July 17 edition of the British journal, The Lancet Infectious Diseases, Dr. Kalil found that the drug reduced the risk of death by 18 percent in the studied patients.

“Even though the company has removed the drug from the market, we should take these results seriously, considering the fact we studied close to 50,000 patients from nine different countries,” Dr. Kalil said. “There’s no other drug for sepsis that works in this way.”

Xigris regulates the body’s inflammatory response to the infection, so that the harmful effect of the response, which is sepsis, is minimized.

The results of the study raise the question if the drug should be put back on the market, as physicians are desperate to find a more effective way to treat sepsis. Currently, antibiotics are the only and most effective drug treatment for sepsis. But even with antibiotics and good medical care, still one-third of patients die.

In the United States, close to 1 million people get sepsis every year. About 300,000 die. As many people die yearly from severe sepsis as do from heart attacks, Dr. Kalil said.

Team develops long-acting nanomedicines for HIV infection

This summer, the Food and Drug Administration approved a daily pill, Truvada, which reduces the risk of HIV infection. Shortly afterward, a UNMC research team’s work to develop weekly or twice-monthly injectable antiretroviral therapy (ART) nanomedicines for HIV patients was published online in the Journal of Infectious Diseases.

A long-acting, nanoformulated ART (nanoART) would be a substantive improvement over daily and sometimes more complex regimen of pills, said Howard Gendelman, M.D., the lead investigator on the development of nanoART for HIV/AIDS and professor and chairman of the department of pharmacology and experimental neuroscience.

The journal article hails the successful testing of UNMC’s ART injectables in the treatment of HIV-infected mice and in preventing new infections.

Rural health is focus of two grants received by UNMC Allied Health program

Improving health care in rural communities will be the focus of two grants received by the School of Allied Health Professions.

The grants, which total almost $1.6 million, will allow UNMC to:

- Host two national conferences geared to physician assistants (PA) and their key role in providing primary care in rural communities; and
- Conduct interdisciplinary research on the prevention of falls in critical access hospitals.

UNMC is one of only 12 universities to receive funding for the Health Resources and Services Administration PA Training in Primary Care grant. The grant provides $993,910 over five years and represents the largest federal grant ever received by UNMC’s physician assistant education program.

The grant’s primary goal is to increase the number of PA graduates in Nebraska who become primary care clinicians, particularly those who will provide care to underserved populations.

The second grant is for $593,088 from the Agency for Healthcare Research and Quality. The primary aim of the grant is to improve patient care and safety by reducing inpatient falls in critical access hospitals that primarily serve rural older adult populations.
Phil Hester didn’t mind shoveling snow, but noticed that he tired easily. He didn’t understand why as he never smoked and was active in sports. At 47, he thought it was age, but a broken rib sent him to the doctor, who was alarmed that Hester’s heart rate couldn’t be detected. An immediate stress test revealed his heart was pumping a mere 12 percent.

“During the test, the nurses watched the monitor and asked how I could even stand up. I wasn’t sure what it all meant,” he said.

Hester was whisked to the emergency room and a three-day hospitalization. His diagnosis: congestive heart failure.

On disability, Hester became involved in a small, preliminary study through the UNMC College of Nursing Lincoln Division to test adherence to exercise in heart failure patients. The pilot study led to a $3.36 million, five-year grant from the National Institutes of Health - National Heart Lung and Blood Institute to analyze long-term adherence to exercise in heart failure patients at Bryan Heart in Lincoln and at Wayne State University and Henry Ford Health System in Detroit.

In heart failure, the heart is weakened over time and can’t pump enough blood to meet the body’s needs. Though the disease is chronic, progressive and incurable, medications and lifestyle change can help people live longer with more active lives. Regular exercise helps patients tolerate more activity, reduce fatigue and improve their mood.

Two groups of randomized patients in the study will receive access to a gym and exercise training. One group will receive additional educational group sessions and support for adherence from an exercise coach.

“Twenty years ago we would have said you shouldn’t exercise, but now we know that exercise is safe and beneficial,” said Bunny Pozehl, Ph.D., professor of nursing in the UNMC College of Nursing-Lincoln Division and principal investigator of the study. “The biggest problem is getting patients to follow an exercise plan. No studies before have focused on this problem.

“Our patients get short of breath, tire more easily and are afraid to initiate exercise. They fear that it will stress their failing heart too much. What they don’t know is exercise is beneficial and will actually help them feel better and have more energy.”

Dr. Pozehl, a nurse practitioner who has worked with the heart failure clinic at Bryan Heart for 17 years, said some of the common barriers to exercise for heart failure patients are the cost of exercise programs and fears that exercise may cause complications. Currently, supervised exercise programs for heart failure patients aren’t reimbursed by most insurance companies and Medicare.

Hester credits exercise and medication for strengthening his heart near normal capacity. “It helped me out a lot and made me feel better. I lost some weight and could breathe easier.”

Strengthening his heart wasn’t the only goal Phil Hester had on his mind when he enrolled in Dr. Bunny Pozehl’s study on heart failure and exercise. He wanted to be strong enough to walk into Heinz Field — home of his beloved Pittsburgh Steelers. He accomplished both goals.
At the University of Nebraska Medical Center we’re No. 6 in primary care education, and we’re climbing. Our novel approaches in this increasingly vital area of medicine have us on the rise, up a spot from a year ago, in U.S. News & World Report’s annual rankings. At UNMC, we educate students and residents to work as teams — with physicians, physician assistants, nurses, pharmacists, public health workers and others. And more than 60 percent of our medical students choose to specialize in primary care. **UNMC. Breakthroughs for life.**