Working to save six million hearts
In this issue of UNMC Discover, we again show the importance of collaboration. Dr. Irving Zucker and his team, Drs. Kaushik Patel and Harold Schultz, have made incredible progress into understanding the relationship between the nervous system and cardiovascular function in heart failure, as verified by the fourth renewal of their Program Project Grant (PPG).

Their accomplishment cannot be overstated. Dr. Zucker’s PPG was one of the first on this campus and remains the longest running. It not only takes a team to obtain and maintain a PPG, but a need to continue to innovate and lead the science. And through this, Dr. Zucker has remained an outstanding mentor to other investigators who are developing their own PPG grants as well.

Drs. Nancy Waltman and Laura Bilek, each with different areas of expertise and members of different colleges, worked together to apply and obtain new grant funding to solve an important clinical problem: osteoporosis after breast cancer.

Dr. Tony Wilson in pharmacology and experimental neuroscience works with Dr. Susan Swindells from internal medicine, to evaluate the effect of aging on HIV-associated neurologic changes. And the list goes on.

UNMC research leaders are committed to reducing barriers to, and incentivizing new collaborations among, all University of Nebraska institutions. Some call this “Team Science,” – a collaborative team of interprofessionals who think about potential solutions to a problem, develop that idea and then conduct research.

Many grants now expect or even require that members of the community also are treated as “members of the team,” if the grant is conducted in the community.

This concept of Team Science requires a shift in culture on many university campuses, not just academic health centers. We need to make sure we value all members of the team, not just the leader, when it comes time for promotions or when our top research awards are evaluated.

It’s important to coach our team leaders to be mindful and to communicate the value of all team members. Team Science is not just about collaborations within UNMC or across the University of Nebraska. It includes teams from across all disciplines and around the world, even with researchers in countries that seem to agree on little else.

As our research community continues to improve how we work together to solve complex problems, teams will be required to include such new or special expertise, as mathematical modeling, engineering and material science.

Key members of those teams will include health care providers and public health practitioners who can bridge the research gap and work with those who know more about patient care or public health improvement. In the end, the goal is to make a difference in people’s lives.

This is one more way that research may be able to change the world.

Jennifer Larsen, M.D.
UNMC Vice Chancellor for Research
ON THE COVER:
Kaushik P. Patel, Ph.D.,
Irving H. Zucker, Ph.D., and
Harold D. Schultz, Ph.D., –
three of the world’s leading
experts on heart failure research.

FEATURES:

4 Heart failure research
expands to brain, kidneys
Studies show that exercise does more
than build muscles. It could save your life.

8 Expert recruits add to
cancer bench strength
World-renowned scientists and physicians
have been recruited to advance cancer
care and research.

10 Dr. Dunaevsky’s brain work
Research explores possible autism link
to infections during pregnancies.

11 Dr. Kielian named
Innovator of the Year
UNeMed honors researcher and inventors.

12 Two unlikely patients
at UNMC
Unlikely patients in the form of
oil paintings were seen at UNMC.

14 Exercise may be possible
solution for bone loss
Vitamins and exercise under study as
interventions to stop osteoporosis in
post-menopausal women with osteopenia.

16 UNMC spinoff company
tests swine flu vaccine
for pigs
New vaccine works by super-charging
the immune system, helping it to more
efficiently target infections.

17 The next BIG little thing
Getting down to the single cell
in single cell genomics.

18 Treatment for inflammatory
bowel disease goes nano
Nanoparticles and microparticles
offer multiple additional advantages
for delivery of drugs in IBD.

19 Aging and the
HIV-infected brain
Interdisciplinary study focuses
on how aging affects cognition.

DEPARTMENTS:

2 Vice Chancellor Message
20 UNMC News
23 Under the Microscope

FOLLOW US: facebook.com/unmcedu twitter.com/unmc youtube.com/unmcedu pinterest.com/unmc
Neurons stained for neurofilaments are isolated from an area of the brain called the paraventricular nucleus that is critical in the regulation of cardiovascular function.

Three UNMC investigators are trying to save six million hearts.

That’s the number of people in the U.S. who suffer from chronic heart failure.

The trio of Irving H. Zucker, Ph.D., chairman, and professors Kaushik P. Patel, Ph.D., and Harold D. Schultz, Ph.D., are three of the world’s leading experts on heart failure. Together, they represent 124 years of research experience.
Dr. Zucker and his team in UNMC’s Department of Cellular and Integrative Physiology want to understand the pathophysiological processes that occur during the progression of chronic heart failure (CHF) with the hope of finding better treatment strategies to improve complications and longevity.

Specifically, they want to provide a comprehensive picture of how CHF augments the response, and enhanced response, of the sympathetic nervous system, which functions like a gas pedal in a car to trigger the body’s fight-or-flight response. To do so, the trio studies three different, but interrelated areas – the heart, brain and kidneys in CHF – and how exercise training affects these mechanisms.

They recently received their fourth, five-year renewal of a Program Project Grant (PPG), unprecedented at UNMC, worth more than $8 million to continue their research into how CHF augments the sympathetic neural function. They’ve been on this quest for the past 16 years.

“The heart is more than a muscle,” Dr. Zucker said. “It’s an intricate nervous system and it makes hormones. It’s not well appreciated because the focus is usually on its main function.”

Heart failure has existed since the days of the Egyptian pharaohs, about 3,500 years ago, and despite the advancement of health care, it continues to be the No. 1 cause of death for men and women worldwide. In the U.S., the disorder annually claims more than 600,000 lives at a cost of more than $100 billion.

Nearly one-half of the deaths from heart disease are due to coronary ischemia that progresses to CHF, the most common diagnosis in hospitalized patients age 65 and older. About one-half of the people who develop heart failure die within five years of diagnosis.

The American Heart Association reports that between 2007 and 2010, 5.1 million Americans over the age of 20 suffered from this malady. By 2030, it is estimated that this number will increase by 25 percent.

The three investigators want to lower those numbers through exercise and new therapies – to provide options that go beyond current therapies that haven’t changed in 30 years.

Knowledge emerging from the PPG, which uses animal models of heart failure, has provided key insights into the neural and molecular mechanisms responsible for impaired autonomic control of the heart and kidneys during the progression of CHF.

The sympathetic nervous system controls unconscious functions of the body and is critical in the regulation of the heart and kidney. This neural system is regulated in at least two regions in the brain, the rostral ventrolateral medulla – a small region of the brainstem – and the paraventricular nucleus (PVN), which is located in the hypothalamus.

Determining the mechanism and therapeutic efficacy of exercise training has been one of the major goals of the grant and the team has demonstrated that exercise training, in animals, reverses the effects of CHF on the sympathetic nervous system.

Dr. Zucker’s team was one of the first to determine some of the mechanisms by which exercise training reduces sympathetic nerve activity in CHF.

Human studies show that exercise improves health 30 percent to 40 percent, and improves five-year survival rate of patients with CHF.

Dr. Zucker has found that exercise training can reduce levels of a molecule – angiotensin II – that plays a key role in heart failure. His team was the first to show that angiotensin II leads to an increase in harmful free radicals in the brain during CHF.

“In heart failure, the body experiences more oxidative stress that produces free radicals (the bad guys) and less antioxidants (the good guys),” Dr. Zucker said. “And these antioxidants aren’t the kind you get from eating blueberries.”

“We have found the origin of chemical changes in the hypothalamus and medulla – regions of the brain that mediate pre-sympathetic neuronal discharge,” Dr. Zucker said. “It’s a truly

Irving H. Zucker, Ph.D.
Harold Schultz, Ph.D., and his research technician, Mary Ann Zink, look at an echocardiogram of heart failure in the left ventricle of a rat’s heart.

Kaushik Patel, Ph.D., and Hong Zheng, M.D., assistant professor, measure neurons in the brain. In the back, Neeru Sharma, Ph.D., assistant professor, shows Andrea Haibara, Ph.D., a visiting associate professor from the Federal University of Minas Gerais, Brazil, how to use a piece of equipment.

integrated system that jumps into sympathetic hyperdrive when heart failure occurs, and where exercise training can play a vital role.”

This integrated system between the heart, brain and kidneys also integrates the three projects in the PPG. The trio believes this is where they can find ways to turn molecular systems on and off to attenuate heart and kidney failure. The key may be two proteins they’ve discovered that act like ‘yin and yang’ during oxidative stress in the central nervous system.

“There is a novel relationship between proteins that promote oxidative stress and those that contribute to antioxidant effects,” Dr. Zucker said. One of the antioxidant transcription factors is called nuclear factor (erythroid-derived 2)-like 2 (Nrf2) and that’s what Dr. Zucker will study in his project “Nrf2: Neuronal Oxidative Stress and Sympathetic Nerve Activity (SNA) in Heart Failure.”

“Figuring out how to activate Nrf2 may be critical to regulating that imbalance in the body,” he said. Dr. Zucker will try to “rescue” animals with CHF by overexpressing Nrf2 in the medulla.

“High oxidative stress occurs when Nrf2, an important promoter of antioxidant enzyme production, is deleted,” he said. “Other data indicates that deletion of this gene results in lower levels of antioxidant enzymes in areas of the brain that regulate SNA to the heart and blood vessels.”

He also is investigating how exercise training in rats with heart failure modulates oxidative stress through this interaction, and is extending previous studies on the role of central angiotensin converting enzyme 2 (ACE2) in activating Nrf2 to reduce oxidative stress.

“What this means for patients is still unclear,” he said, “but there are techniques that have been shown to increase Nrf2, such as exercise training.”

As CHF progresses, blood supply to tissues is reduced. Fluid regulation is compromised and the kidneys begin to retain salt and water. The resulting edema puts more stress on the heart.

For the past 30 years, Dr. Patel has been interested in the role of the PVN in the regulation of the circulation and renal function. In his project, “Activation of the PVN in Heart Failure: Role of HIF1-α, and Renal Afferents,” he studies the basic
PPG HAS A FAR REACH

Irving H. Zucker, Ph.D., chairman of the Department of Cellular and Integrative Physiology since 1989, has been director of the Program Project Grant from the National Heart, Lung, and Blood Institute – a division of the National Institutes of Health since its inception in 1999. When completed, it will bring total funding from the PPG to more than $32 million. This is the longest continuously funded PPG at UNMC.

A PPG provides support for integrated research projects involving a number of independent investigators who share knowledge and common resources. Each project is directly related to common themes of the total research effort, in a well-defined integrated research program goal. Added value comes from common cores that are funded as part of the PPG.

“Our theory is that if you cut renal nerves, you prevent this vicious cycle,” Dr. Zucker said.

Then, there is the exercise component. “The hormones that control water and salt retention are the same that regulate blood pressure,” he said. “We have shown that exercise training allows for better function of the kidneys and improves the overall circulation and heart function.”

In the third project, “The Chemoreflex in Heart Failure,” Dr. Schultz explores the role of impaired blood flow on abnormal reflex control of the heart, kidneys and breathing in CHF.

“The problem of exercise with heart failure is that breathlessness limits exercise tolerance. Carotid body sensors mediate the sensation of breathlessness, or air hunger, which can impair exercise capacity,” Dr. Schultz said.

“The oxygen sensors in the carotid body become overly active in heart failure due to the inability of the failing heart to maintain adequate blood flow and oxygen delivery to the sensors. We are finding that selective interruption of this signal from the carotid body by surgical ablation or by exercise training improves breathing.”

Dr. Schultz’s work also has shown that abnormal carotid body stimulation increases sympathetic outflow to the kidney, which then increases salt and water reabsorption and an expansion of blood volume that the failing heart cannot adequately pump.

The project recently has shown that ablation of the carotid body improves the function of the kidneys and heart leading to greater survival in heart failure animals, which could have a translational impact for patients. Results from these studies have served as the basis for a recent ongoing clinical trial in humans.

Drs. Zucker, Patel and Schultz serve on numerous editorial boards of medical journals, lecture around the world and present papers to their peers. A small department by national standards, UNMC’s Department of Cellular and Integrative Physiology’s reputation stands tall internationally.

“Now when we stand up at meetings and say we’re from Nebraska, people know where that is,” Dr. Zucker said. 

principles underlying intercellular communication between preautonomic PVN neurons to determine how changes within the PVN contribute to enhanced sympathetic drive in CHF.

He also will explore the novel idea that sensory nerves originating in the kidney negatively influence neural control of circulation in CHF and contribute to that downward cycle of free radical production.

“Our theory is that if you cut renal nerves, you prevent this vicious cycle,” Dr. Patel said.

Then, there is the exercise component. “The hormones that control water and salt retention are the same that regulate blood pressure;” he said. “We have shown that exercise training allows for better function of the kidneys and improves the overall circulation and heart function.”

In the third project, “The Chemoreflex in Heart Failure;” Dr. Schultz explores the role of impaired blood flow on abnormal reflex control of the heart, kidneys and breathing in CHF.

“The problem of exercise with heart failure is that breathlessness limits exercise tolerance. Carotid body sensors mediate the sensation of breathlessness, or air hunger, which can impair exercise capacity,” Dr. Schultz said.

“The oxygen sensors in the carotid body become overly active in heart failure due to the inability of the failing heart to maintain adequate blood flow and oxygen delivery to the sensors. We are finding that selective interruption of this signal from the carotid body by surgical ablation or by exercise training improves breathing.”

Dr. Schultz’s work also has shown that abnormal carotid body stimulation increases sympathetic outflow to the kidney, which then increases salt and water reabsorption and an expansion of blood volume that the failing heart cannot adequately pump.

The project recently has shown that ablation of the carotid body improves the function of the kidneys and heart leading to greater survival in heart failure animals, which could have a translational impact for patients. Results from these studies have served as the basis for a recent ongoing clinical trial in humans.

Drs. Zucker, Patel and Schultz serve on numerous editorial boards of medical journals, lecture around the world and present papers to their peers. A small department by national standards, UNMC’s Department of Cellular and Integrative Physiology’s reputation stands tall internationally.

“Now when we stand up at meetings and say we’re from Nebraska, people know where that is,” Dr. Zucker said. 

web extra unmc.edu/discover Learn more about UNMC’s cardiovascular research.
When finished, the Fred & Pamela Buffett Cancer Center will be a world-class research and patient care center – not just because of the excellent facility, but also because of the world-renowned scientists and physicians who have been recruited to advance cancer care and research.

Like Michael Green, Ph.D. An assistant professor in the Eppley Institute, he began his UNMC career on the heels of a major contribution to a breakthrough in Hodgkin lymphoma treatment. Clinical trial results for the new therapy inspired by his research were detailed in a December 2014 edition of The New England Journal of Medicine.

While a postdoc at Dana-Farber Cancer Institute in Boston in 2010, Dr. Green was first author on the discovery of a therapeutic target – a gene whose increased expression allows cancer cells to evade detection and eradication by the immune system.

Expression of this gene may be why Hodgkin relapse rates can be as high as 25 percent.

“Ligands on the tumor cell surface bind to their receptors on T-cells, blocking their normal function,” Dr. Green said. “The natural role of these molecules is to decrease the immune response after an infection has been cleared. But cancer cells hijack it so they can shut down an anti-tumor immune response.”

Thankfully, there was a potential neutralizing antibody already in clinical trials. So a study involving patients with relapsed or refractory lymphoma got to skip straight to Phase II, to “a pretty remarkable result,” Dr. Green said. The treatment was awarded breakthrough therapy designation by the FDA. By the time the clinical trial started in 2011, Dr. Green already had left for Stanford University, but still feels very satisfied with the end result.

“That’s why we do what we do,” he said. “Publications and grants are nice, but this is the real reason behind our research.”

At Stanford, Dr. Green turned his attention to the as-yet incurable follicular lymphoma. And there is no better place to continue this research, he decided, than at UNMC, where Jim Armitage, M.D., and Julie Vose, M.D., head up a world-renowned lymphoma study group.

“That was imperative in coming here,” he said. “Laboratory research is only as good as the difference that it makes to patients. Here we have a superb clinical team, so we can effectively translate research from the laboratory to the clinic in the form of new treatment strategies, and we also can use laboratory research to understand the diverse outcomes with current treatments.”

Also helpful is the relationship history of the patients who donated tumor tissue.

Now, Dr. Green is studying a novel gene mutation that helps follicular lymphoma cells evade the immune system. “We have defined the mutation we want to target, so now we are trying to identify a specific therapy – it is a great example of ‘precision medicine.’”

Read about the clinical trial.
Read Dr. Green’s research article on a new therapy target.
Learn more about UNMC’s core facilities.
Read Dr. Green’s journal article on follicular lymphoma.
A NEW RECRUIT COLLABORATION

Dr. Green has teamed with Matthew Lunning, D.O., a fellow new recruit to the Fred & Pamela Buffett Cancer Center. Together, they formed the Lymphoma Precision Medicine Laboratory, a multi-disciplinary lab with both a clinical and research focus. It operates as part of the Dr. James O. Armitage Center for Leukemia and Lymphoma Research.

“Our goal is to apply molecular laboratory research to better understand and target therapies in lymphoma,” Dr. Green said. “As part of this effort, we are performing scientific correlates along with clinical trials to identify biomarkers that can be used in the future to target the next generation of lymphoma therapies specifically toward patients who are most likely to benefit.”

Drs. Green and Lunning also are attempting to re-evaluate the approach used for lymphoma classification – so as to better classify patients into groups more likely to respond to similar therapies. To do so, they’ll incorporate information from genetic alterations that directly drive the disease. Patients with similar genetic alterations will be grouped together.

They’ll take advantage of the Nebraska Lymphoma Study Group’s tissue bank: “It has thousands of tumors that we can evaluate for genetic mutations and identify groups with similar genetics and clinical behavior,” Dr. Green said. “The aim is to pave the way for future therapeutics to be developed for these genetic subtypes that specifically address the etiology of the disease, so that patients can be treated using a ‘precision medicine’ approach based upon their individual tumor’s molecular characteristics.”

It’s collaborations like this at UNMC that allow innovation to happen.

Cancer center draws recruits

Michael Green, Ph.D., and Matthew Lunning, D.O., are among more than two dozen new recruits hired since January 2014, when excavation work began on the site of the new Fred & Pamela Buffett Cancer Center.

“From the start, we’ve been committed to attracting the best physicians and researchers who are at the forefront of cutting-edge, compassionate cancer research,” said Kenneth Cowan, M.D., Ph.D., professor of oncology at the Eppley Cancer Institute and director of the Fred & Pamela Buffett Cancer Center. “And, we will continue to do so after the cancer center opens in 2017.”

Joining the ranks thus far, are the following:

Sarah Thayer, M.D., Ph.D., chief of the division of surgical oncology, associate director for clinical affairs and physician-in-chief of the Fred & Pamela Buffett Cancer Center

Lyudmyla Berim, M.D., internal medicine - oncology/hematology
Krishna Gundabolu, M.B.B.S., internal medicine - oncology/hematology
Matthew Lunning, D.O., internal medicine - oncology/hematology
Pavankumar Tandra, M.D., internal medicine - oncology/hematology
Vijaya Bhatt, M.D., internal medicine - oncology/hematology
Chi (Kevin) Zhang, M.D., radiation oncology
Nicole de Rosa, M.D., surgical oncology
James Padussis, M.D., surgical oncology
Michael Green, Ph.D., Eppley Institute
Aaron Mohs, Ph.D., pharmaceutical science
Farryl Bertmann, Ph.D., Health Promotion, Social and Behavioral Health, College of Public Health
Punita Dhawan, Ph.D., biochemistry and molecular biology
Amar Singh, Ph.D., biochemistry and molecularly biology
Rebecca Oberly-Deegan, Ph.D., biochemistry and molecular biology
Nicholas Woods, Ph.D., Eppley Institute
Martin Conda-Sheridan, Ph.D., pharmaceutical science
Dr. Dunaevsky’s brain work

For Anna Dunaevsky, Ph.D., it’s all about the brain.

Dr. Dunaevsky, an associate professor of developmental neuroscience, has always been fascinated by the brain – specifically “how this complex structure is developed.”

From there, it was a short step to connect behavioral changes with structural development and actual cellular events. That step became inevitable when she joined the Munroe-Meyer Institute, where she took an interest in questions related to neurodevelopmental disorders.

One of those questions – the effects of maternal inflammation on developmental disabilities, specifically autism – led to Dr. Dunaevsky’s four-year, $1.5 million grant from the National Institute of Mental Health for a project titled “Maternal Immune Activation in a Genetic Mouse Model of Autism Spectrum Disorder.”

The project explores maternal infections during pregnancies as a risk factor that increases the chance of offspring developing autism.

Dr. Dunaevsky is building on three lines of evidence:

- Research has shown that infection during the first or second trimester, either viral or bacterial, is a risk factor for autism.
- There is evidence that autistic patients show increased levels of such inflammatory molecules as cytokines.
- Animal studies have shown that when inflammation is induced in a pregnant mother, offspring display various behavioral alterations that are relevant to autism – reduced ultrasonic vocalization, which is a form of communication, increased repetitive behavior, and reduced social interaction – that suggest changes in the brain.

“All of that has led us to suggest that maternal immune activation, which is what we call this model, leads to alterations in development of synapses, the connections between neurons.”

Dr. Dunaevsky continues work that was initially funded by the Nebraska Research Initiative and the Department of Defense.

“We found that impairments in synapses – in terms of numbers and function – correlate with the behavioral deficits that we see,” she said.

Importantly, Dr. Dunaevsky and her team found that, where there is an increased inflammatory state in the brain of the mouse offspring, a two-week anti-inflammatory treatment led to reversal of the synaptic impairments and some of the behavioral impairments in young mice.

“In adult mice, that early, short-term treatment had some beneficial effect, but it didn’t completely reverse the impairments,” she said.

“There are many mothers who get sick during pregnancy and their children do not develop autism,” Dr. Dunaevsky said. “And of course, there is plenty of genetic evidence for involvement of neuronal genes in autism, so just immune activation is not the entire story. It’s therefore likely that interactions with genetic risk factors are involved.”

That is the focus of the new project — to explore the genetic risk factors in combination with environmental risk factors.

“That component of the anti-inflammatory treatment was surprising to us, how effective it was in mice,” she said. “So with this new grant, we’re going to use this approach as well.”
Tammy Kielian, Ph.D. – honored in 2012 as the Emerging Inventor – was named the 2015 Innovator of the Year during UNeMed’s annual Research Innovation Awards ceremony in October. UNeMed is UNMC’s technology transfer office.

Dr. Kielian, the Choudari Kommineni, D.V.M., Ph.D., Professor of Pathology in pathology and microbiology, is the first two-time winner of a major UNeMed award in the nine-year history of the program.

Her work on a potential cure for juvenile Batten disease and treatments for S. aureus biofilms made her an easy choice for the top award in 2015, said Michael Dixon, Ph.D., UNeMed president.

“Dr. Kielian is exactly the kind of scientist we love to celebrate during Innovation Week,” Dr. Dixon said. “Every day, she and her team do what it takes to move the science forward, and help us push her research into the real world where it has a chance to not just save lives, but save families.”

Her team is on the verge of clinical trials for two ways to fight juvenile Batten disease, a rare and fatal childhood neurodegenerative disease. One approach treats the disease using an existing class of drugs, but the other, a gene therapy treatment, is a potential cure.

In addition to this work, Dr. Kielian developed a new strategy for targeting the immune system to help prevent and treat Staphylococcus aureus biofilm infections.

UNeMed also honored all UNMC personnel who submitted a new invention, received a U. S. patent or licensed a technology. The Most Promising New Invention of 2015 was awarded to Michael Wadman, M.D., and Thang Nguyen, both of emergency medicine, for their innovative concepts of wound irrigation and oral airway management.

The irrigation system adjusts and maintains consistent pressure with solution to clean almost any wound. An airway management system, for emergency care providers, is still under development.

The awards ceremony was the culmination of Innovation and Research Week, a series of events to showcase and celebrate UNMC discoveries. 

Dr. Tammy Kielian – UNeMed’s 2015 Innovator of the Year.

Dr. Michael Wadman and Thang Nguyen.

Dr. Michael Wadman and Thang Nguyen.
Two unlikely patients at UNMC

by Elizabeth Kumru

Two oil paintings from the Joslyn Art Museum by renowned artists of the 18th and 19th centuries have been unlikely patients at UNMC.

James Temme, associate professor and director of the radiation science technology division in UNMC’s College of Allied Health Professions, was called on last year by the Joslyn and the Nebraska State Historical Society’s Gerald Ford Conservation Center to help with conservation efforts. They wanted the paintings X-rayed to allow them to learn more about the artists’ techniques and the condition beneath the surface of these well-known artworks.

The first patient, “The Pearl of Venice,” by Thomas Moran, dated 1899, has long been a favorite not only of Joslyn visitors, but of the artist himself, who considered it his finest view of the city. The X-ray revealed Moran’s underdrawing, and was part of a behind-the-scene conservation exhibit at Joslyn.
The second patient, “Marquesa de Fontana,” was painted around 1800 by Spanish court painter Francisco de Goya, and X-rayed in October 2015. Kenneth Bé, paintings conservator at the Ford Center, said radiographic imaging allows him to see more details than he can with the naked eye or even a microscope. Art restoration was the topic of one of UNMC’s Science Cafés.

“It is only with this kind of imaging that one can truly know certain aspects about a painting hidden beneath the surface, such as some condition problems and clues to the painter’s studio technique,” Bé said.

“As for the Goya, much of the painting has been restored and there are areas that are difficult to study because of the restoration paint. Radiography will help us better understand the nature of parts of the original painting which are extant but not necessarily visible on the surface,” Bé said.

Temme is proud that UNMC can provide such service to the art community. “The radiographic images of these paintings are works of art by themselves. The prints of these images could be displayed in anyone’s home or office.”

Learn more about the Science Café.

Watch past podcasts of UNMC’s Science Café.
Nancy Waltman, Ph.D., has been sounding the alarm to women for years about the dangers of osteopenia – early bone loss – which can lead to osteoporosis.

Statistics say 18 percent of women with osteoporosis, a disease of decreased bone strength and low bone mineral density, suffer a hip fracture and 22 percent die within a year of their fracture.

“There’s very little publicity about osteoporosis, yet it’s one of the major causes of death and disability in women,” said Dr. Waltman, a professor in the College of Nursing-Lincoln Division. “Women enrolling in our studies tell me that they weren’t aware they were at risk for bone loss, and they didn’t realize how frequently women with bone loss suffer complications like fractures.”

In 2002, she received her first major funding from the National Institute of Nursing Research/National Institutes of Health (NIH) to test interventions promoting bone health in postmenopausal women.

Dr. Waltman and Laura Bilek, Ph.D., associate professor, physical therapy, College of Allied Health Professions, are now principal investigators of a $3.2 million NIH grant testing interventions for preventing further bone loss and osteoporosis in post-menopausal women with osteopenia. Prevention treatments are important since during the first five years after menopause women lose 2 percent of their bone mineral density each year.

“It’s a fairly new idea, both on the federal level and at UNMC, to have two principal investigators from different disciplines who are equally in charge of a federally funded grant,” Dr. Waltman said. “I know we wouldn’t have been funded otherwise. Our contributions together are essential.”

Women are randomly assigned 12 months of one of three treatments: calcium and vitamin D only; a bisphosphonate plus calcium and vitamin D; or a structured exercise program plus calcium and vitamin D.

For the five-year study, Dr. Bilek designed an exercise program for one arm of the study.

One of their hypotheses: Exercise may more effectively improve bone structure than either bisphosphonates or calcium and vitamin D alone.

Though exercise is one of the most useful tools to prevent bone loss, it also is the biggest obstacle, Dr. Waltman said.
“Exercise is the magic pill, but most people don’t adhere to exercise,” she said. “The side effects of exercise are that it lowers blood sugar and blood pressure, decreases weight, increases energy and improves mood. We need more studies on exercise adherence.”

Dr. Bilek said many women think about exercising for reasons such as cardiovascular health but don’t consider their bones.

“But walking alone is not enough to improve bone health. It is important to add exercises such as weight lifting, jump roping or hiking.”

For more information about the study, call 402.559.6584 or email hops@unmc.edu.
A “swine flu” H1N1 vaccine developed at UNMC soon will enter a definitive round of testing, where researchers hope to establish its ability to ward off the virus in pigs.

Made possible by a licensing deal brokered through UNMC’s technology transfer office, UNeMed Corporation, the study will evaluate the vaccine on 30 to 40 pigs.

If results are positive, Prommune, Inc. could begin offering an H1N1 vaccine to hog farmers as early as the end of the year – although full approval from the USDA would likely take up to four years.

Ultimately, an H1N1 vaccine as potentially effective as Prommune’s could dramatically diminish the virus as a global threat to the world’s pig population, and could even lead to more effective vaccines for similar diseases in birds and perhaps humans.

Sam Sanderson, Ph.D., founded the company in 2002 and is a research associate professor of pharmaceutical science in UNMC’s College of Pharmacy.

Dr. Sanderson’s technology essentially helps activate and direct the immune system into a more targeted and efficient attack against invading pathogens.

The technology, an immune stimulating peptide called EP67, is a “platform technology” that is so versatile it can be tweaked and modified to work against a number of ailments and in a wide variety of animals. In addition to the H1N1 vaccine, EP67 could have applications against different varieties of the avian flu virus, antibiotic-resistant bacteria and other infectious agents.

But long before Prommune can develop anything for human use, researchers still need to compile years of data that include results of the current trials, said Prommune’s interim CEO Sam Al-Murrani, Ph.D.

Dr. Al-Murrani, who has a background in animal health and holds a doctorate in immunology and biochemistry, joined Prommune in March after first meeting Dr. Sanderson at an animal health investment forum in Kansas City in 2013.

He said a platform technology like EP67 would intrigue investors and strategic partners. Several recent initial public offerings in the animal health sector didn’t compare well to Prommune’s innovative technology, he said.

“I think Prommune today has more product and market potential than any of those companies,” he said.

Dr. Al-Murrani is the chief executive officer of Babylon BioConsulting, a firm based in Cheyenne, Wyo., which specializes in bringing early-stage technologies to biomedical markets.

Since signing on with Prommune, Dr. Al-Murrani has helped build a corporate structure, negotiated the licensing deal with UNeMed and established a strategic alliance with a nationally renowned animal testing facility that helped open the door to the upcoming trial.
It's the latest in cutting-edge technology in single cell genomics.

And even though it doesn't look like much – a blue inconspicuous machine with a touchscreen of buttons and blinking lights – the information it can extract from a single cell is beyond amazing.

As recently as last year, a researcher who wanted to know what genes were important in a particular tumor would only be able to get a general idea of the tumor's composition with the help of high-throughput gene expression profiling methods.

But researchers want more specific information.

"Typically a researcher analyzes a DNA/RNA sample extracted from a mixture of millions of cells, but so much more detailed information can be gleaned by analyzing the DNA/RNA from individual cells," said Jim Eudy, Ph.D., director of the next generation DNA sequencing core facility.

Now, thanks to a $500,000 grant from the Nebraska Research Initiative, researchers at UNMC will be able to do just that.

With the C1 Single-Cell Auto Prep Integrated Fluidic Circuit, researchers now have the capability of deciphering the differences in groups of cells that appear similar but possess fundamentally different properties.

The journal *Nature Genetics* deemed single cell genomics the “Method of the Year” in 2014 and called it a turning point poised to transform many areas of biology and medicine.

"It's the next big little thing," Dr. Eudy said. "Single cell genomics technology is revolutionary."

There is currently no other single cell genomics instrumentation in the state, he said, adding that the new technology will be used as part of an interdisciplinary team combining the expertise of the genomics, flow cytometry, confocal imaging and bioinformatics core facilities, he said.

Hamid Band, M.D., Ph.D., director of the center for breast cancer research and associate director for translational research in the Eppley Institute at UNMC, said that because cancer cells exhibit a tremendous amount of cellular heterogeneity or diversity, the biological differences between those cells can be obscured using traditional sequencing methods.

Single cell genomics technology allows researchers a window into the mutational status and epigenetic landscape of individual cells that allows them to see such key properties of tumors as why some stay dormant for a long time only to recur years later, Dr. Band said.

"This will allow physicians to have advance information on which drugs will likely work as second or third line therapies in patients whose cancers recur."
The 1.4 million predominantly young adults in the United States affected by inflammatory bowel disease (IBD) need help. The disease is bad enough – it includes chronic inflammation of the gastrointestinal (GI) tract that comes and goes. It’s painful, debilitating and comes with an increased risk of colon cancer.

IBD, not yet fully understood, has no permanent cure. Some agent or a combination of agents – bacteria, viruses, antigens, or even the body’s own tissue – triggers the body’s immune system to produce an inflammatory reaction in the intestinal tract.

Annual health care costs are more than $1.7 billion in the U.S. Treatment is palliative and lifelong. Biotechnological advances have brought new treatments – but these can be nearly as bad as the condition itself.

Antibody-based treatments for IBD have to be given by injection and can be associated with severe side effects like Cushing’s syndrome, diabetes and osteoporosis. Not to mention the risk of infection.

Thank goodness for the drug delivery capabilities of particles. Thank goodness the UNMC College of Pharmacy is on the case.

David Oupicky, Ph.D., professor of pharmaceutical sciences and co-director of the Center for Drug Delivery and Nanomedicine (CDDN), leads an effort on the development of a novel combination therapeutic strategy for an oral treatment of IBD based on particles recently developed in his lab.

There have been some challenges. Thanks in part to the problems presented by antibody-based treatments, the oral route is considered ideal for IBD treatment due to high patient compliance and direct access to the disease site. But, high enzymatic and nuclease activity, extreme pH conditions, and the physical mucus-epithelial barrier – all the acids and digestive enzymes in the stomach – can make oral treatments tough.

IBD can change the GI environment, affecting the efficacy of traditional drug delivery methods.

Again, thank goodness for nanoparticles.

“Particle formulations can extend the time the encapsulated drugs spend in the system,” Dr. Oupicky said. “The use of mucoadhesive polymers, like chitosan, can further enhance time the drug stays in the GI tract to provide sustained release of active agents in the mucosa layer.”

Because of their ability to target sites of intestinal inflammation, nanoparticles and microparticles offer multiple additional advantages for delivery of drugs in IBD. Through chemistry, treatment can be selectively delivered to inflamed intestinal tissue either by “passive” or “active” targeting.

“Passive targeting takes advantage of the size-selective accumulation of particles in the gastrointestinal inflammation sites,” Dr. Oupicky said. Active targeting to selected sites and cells in the GI tract can be achieved by conjugation of specific ligands to the surface of the particles.

They are not there yet. But, Dr. Oupicky, the CDDN, and the College of Pharmacy, are working to help millions of people who suffer from this debilitating disease.
How aging affects cognition in HIV-infected patients has been the focus of a three-year interdisciplinary research effort led by Tony Wilson, Ph.D., and Susan Swindells, M.B.B.S.

Now, with the help of a $2.2 million, five-year R01 grant received in 2014 by Dr. Wilson from the National Institutes of Health, they have expanded their efforts to understanding how HIV affects that aging process and what might be done early on to decrease the risk that people with HIV will develop cognitive impairments. Dr. Wilson is associate professor of pharmacology/experimental neuroscience and neurological sciences.

“One of the problems with this cognitive impairment is that it’s very difficult to measure,” said Dr. Swindells, the HIV Clinic Medical Director. “It’s difficult to see what’s going on in the brain. Studies with autopsies have been done, but those are challenging.”

The magnetoencephalography (MEG) scanner in Dr. Wilson’s laboratory is capable of charting brain function in HIV-infected patients (and healthy controls), offering an exploratory avenue that has been paying dividends for the scientists’ collaboration.

“Originally, we were looking at how aging affects brain function in HIV-infected patients, focusing on older patients,” Dr. Wilson said. “Getting this large grant allowed us to look at the whole aging process. Now we are recruiting more than 200 participants who are from age 22 to 76.”

Dr. Swindells said the team drew on a grant that Howard Fox, M.D., Ph.D., received for his Chronic HIV Infection and Aging in NeuroAIDS (CHAIN) Center for the initial work, which in turn led to Dr. Wilson being awarded this new grant.

The clinical application will be to re-scan the same individuals using the MEG to see if brain function has degenerated, improved or stayed the same.

“The problem is there’s no good biomarker,” Dr. Swindells said. “We need a way to measure this process, not only to stage it in an individual patient, but also to look at treatment response and, for clinical trials, to see if a treatment is successful. We need some way to measure, ‘Is this working or not?’ That’s the area where the MEG may have an important role.”

Dr. Swindells’ skills as a clinician and a researcher have been integral to the project, Dr. Wilson said.

“Dr. Swindells and I have very different expertise,” he said. “She knows a lot about HIV infection and has studied the epidemic since it first began. She has just been phenomenal in explaining how HIV infection works and the key issues involved. She had a huge role in mentoring me into a higher-level scientist, a more mature scientist.

“We also have had a great participation rate from Dr. Swindells’ patients and community volunteers,” he said. “The community plays a major role in the success of studies like this, and so far we have had many healthy adults volunteer to be in the study as controls. The MEG is totally harmless, and they seem to find the experience totally fascinating.”

Read more about the study.

by John Keenan
UNMC, NSRI team for biodefense research

The National Strategic Research Institute (NSRI) at the University of Nebraska, a university-affiliated research center (UARC), has been awarded a $5.3 million contract from the United States Army Medical Research Institute of Infectious Diseases (USAMRIID).

The award will allow a UNMC research team with significant experience to conduct research on current and emerging biodefense threats. The results will provide medical solutions to protect warfighters.

Ken Bayles, Ph.D., associate vice chancellor for basic science research at UNMC and project initiator for the research contract, said, “This is the first step in creating a sustainable partnership between USAMRIID, UNMC and NSRI that includes the hiring of an infectious disease research specialist, along with five additional support personnel.

“Combined, these researchers will bring to UNMC a solid foundation of expertise in the use of next generation sequencing technologies to study highly infectious pathogens such as Ebola.”

Dr. Bayles and the UNMC research team will work closely with Mariano Sanchez-Lockhart, Ph.D., a renowned USAMRIID research scientist. USAMRIID is the lead Department of Defense laboratory working with highly dangerous biological select agents and toxins. Dr. Bayles said the award is a clear vote that USAMRIID recognizes the expertise and significant resources available at NSRI/UNMC in infectious disease research.

“The key role UNMC played in the United States 2014 Ebola epidemic response is only the beginning to what our researchers and clinicians can contribute to this field,” Dr. Bayles said.

Study explores help for Alzheimer’s, dementia caregivers

Steve Bonasera, M.D., Ph.D., associate professor of geriatrics at UNMC, is co-investigator of a $10 million grant with the University of California San Francisco supporting a study to bring respite to caregivers.

“There are Nebraska family members who care for loved ones with Alzheimer’s or dementia who are going it alone with little or no resources or training,” Dr. Bonasera said. “The study provides the opportunity for caregivers to be networked with advice, expertise and resources from some of the top specialists in the world in Alzheimer’s and dementia.

“Some caregivers are really stressed out. We will find out what needs they have, teach them what to expect and put together a plan on how to work with their health providers.”

The grant, awarded by the U.S. Centers for Medicare & Medicaid Innovation, created a family-centered model that provides around-the-clock online education and consultation for patients with Alzheimer’s disease and their caregivers. It uses phone- and web-based tools. Some patients will use remote monitoring with smart phones and home sensors.

The study will compare the current standard of care model, using caregivers in a control group, to the new model being used in the study. The goal is to determine if the new model improves the quality of life of both patients and caregivers. The hope is that the interventions will keep people with dementia at home longer and at the same time lower family and caregiver stress.

The model, called Dementia Care Ecosystem, will not replace clinicians, but rather will deliver to patients and their families educational resources developed over the past decade by UCSF’s Memory and Aging Center and UNMC physicians.

For information about the study, contact Jackie Whittington at 402.559.6117 or jwhittin@unmc.edu.
UNMC initiates new ophthalmology journal

UNMC initiated a new open-access online-only journal, the American Journal of Ophthalmology Case Reports, in December to be published by Elsevier, a world-leading provider of scientific, technical, and medical information products and services. It is a companion publication to the prestigious American Journal of Ophthalmology.

The editorial office, housed at Truhlsen Eye Institute (TEI), is run by editor-in-chief Quan Dong Nguyen, M.D., chairman of the UNMC Department of Ophthalmology and Visual Sciences and director of TEI, and Anna Boyum, Ph.D., a neuroscientist and 2013 graduate of UNMC, has been chosen as the managing editor.

“Part of this is being the person who has the research questions unless you’re the clinician who is seeing the patients,” he said. “We approached the investigators about being a part of the consortium, because combined, UNMC and Children’s Hospital & Medical Center, we’re one of the largest OI clinics in the country.”

The new journal welcomes the submission of original, previously unpublished case reports directed to ophthalmologists and visual science specialists,” Dr. Nguyen said.

Dr. Nguyen assembled an esteemed editorial board for the journal, which consists of national and international leaders in different areas of ophthalmology who have published extensively, including: Vikas Gulati, M.D., associate professor of ophthalmology and director of the glaucoma service at TEI; and Diana Do, M.D., professor of ophthalmology, director of the Carl Camras Center for Innovative Clinical Research in Ophthalmology at TEI, and an international leader in retina diseases.

“The cases presented in the journal will be challenging and stimulating, and presented in an educational format to engage the readers as if they are working alongside the caring clinician-scientists,” Dr. Nguyen said.

Submissions are to be clear, concise, and well-documented reports. Brief reports, case series, meta-analyses, and editorials on specific themes also are welcome, he said.

“Our hope is for the journal to serve as a dedicated forum for clinician scientists around the world to share relevant information on the diagnosis and management of the most difficult cases that they encounter in their daily practice, as well as to provide insightful clinical pearls,” Dr. Nguyen said.

UNMC, Children’s team on NIH brittle bone study

UNMC and Children’s Hospital & Medical Center have been designated as a joint site for a National Institutes of Health (NIH) study to chart the progression of the brittle bone disease osteogenesis imperfecta (OI).

The study marks UNMC’s/Children’s first NIH-backed study on OI since it was accepted into the national Rare Disease Clinical Research Network.

Membership in the consortium, which began in July, puts UNMC and Children’s on the cutting edge of brittle bone research, said Eric Rush, M.D., assistant professor at UNMC’s Munroe-Meyer Institute, pediatric geneticist at Children’s and primary investigator for the study’s Omaha site.

“All of the major OI centers around the country are part of this consortium,” he said. “We approached the investigators about being a part of the consortium, because combined, UNMC and Children’s Hospital & Medical Center, we’re one of the largest OI clinics in the country.”

“Now the research piece is coming online for us,” Dr. Rush said. “We’re starting to do more research, so all different facets of brittle bone diseases – care, research and education – are going to be done here at UNMC and Children’s.

“It’s very exciting to get a clear picture for what the natural history of these diseases are, which we don’t completely understand, especially as people age.”

Being one of the sites for an NIH-funded multi-center trial not only recognizes UNMC’s leadership in this rare bone disease, but its growing reputation in rare genetic diseases in general, said Jennifer Larsen, M.D., vice chancellor of research.

“For rare diseases, it is important to collaborate with other centers,” Dr. Larsen said. “This trial also provides an opportunity for our patients to help understand and better chart the future of management and outcomes of this rare bone disease.”

UNMC’s Munroe-Meyer Institute may become involved with companion studies as part of the consortium, Dr. Rush said.

“One of the things MMI has always believed in is really transformative care, and that is one of the things Chancellor (Jeffrey) Gold has discussed as well,” Dr. Rush said.

“That’s really what we’re trying to do – transformative care. To truly transform that care, you not only need the clinical piece and the bedside (care), but you need to be involved with the research aspects as well. That’s one reason why MMI and UNMC/Children’s is a good fit for this.”

Clinical expertise also offers another advantage, he said – knowing what questions to ask.

“It’s hard to develop really good clinical research questions unless you’re the clinician who is seeing the patients,” he said. “Part of this is seeing where the gaps exist. Part of this is also being the person who has to say, ‘I don’t know’ when you’re asked by parent or patient.”

UNMC discover
UNMC research team lands $8.8 million NIH grant

UNMC research team has been awarded a five-year, $8.8 million grant from the National Institute on Drugs of Abuse-National Institutes of Health for their work on HIV/AIDS treatment and eradication.

The goal of the research is to develop a long-acting antiretroviral therapy that could be taken once every six months to provide chemical viral eradication. The work, if realized, could represent a major breakthrough for HIV/AIDS patients, who currently have to take one pill each day.

Antiretroviral therapy (ART) has revolutionized HIV treatment, said Howard Gendelman, M.D., professor and chair of the UNMC Department of Pharmacology and Experimental Neuroscience. Drugs are combined that attack the virus at different stages of its reproductive cycle. ART doesn’t cure HIV, but it stops it from spreading.

The goal of ART is to get the viral load in the blood stream so low that tests can’t even detect it. HIV is still there, but there’s not enough of it to cause symptoms — as long as patients keep taking their medications.

“Dr. Gendelman continues to drive the science to improve ART therapy,” said Jennifer Larsen, M.D., vice chancellor for research.

Working with two major pharmaceutical companies, the UNMC scientists have packaged antiretrovirals into targeted nanoparticles, which can improve drug biodistribution and target sites where the virus hides.

A prime directive for the work is to bring the drug to sites where the virus hides and to combine ART with other medicines that work to destroy whatever virus remains in the body.

“It’s a sort of seek and destroy mission for the research,” said Dr. Gendelman, who noted that preliminary test results in animal models have been promising.

He said the long-term goal of the research is to enable a new product. Under development is a nanomedicine good manufacturing facility on the UNMC campus, which would develop formulations for phase I clinical testing.

Dr. Gendelman’s research team has exceeded $20 million in active funding largely focused on nanomedicines. Since 2010, the combined research efforts of the research team have led to 10 other grants totaling more than $12 million.

Clinical trials pave way for new medicines

As the state’s only public academic medical center, UNMC, and its primary clinical partner Nebraska Medicine, offer patients with life-threatening diseases unique, cutting-edge treatments that aren’t found anywhere else.

Before a new drug comes on the market, it must first pass through rigorous cellular, animal and finally human testing – or clinical trials. Clinical trials determine how well new medical approaches work in people. Each study attempts to answer scientific questions and tries to find better ways to prevent, screen for, diagnose or treat a disease. Clinical trials also may compare a new treatment to a treatment already available.

To learn what studies are available or to get more details about a particular study, visit www.unmc.edu/clinicaltrials, or contact the Research Subject Advocate Office at 402.559.6941 or unmcrsa@unmc.edu.
Aging can be an unpleasant process. Not only can it be a disappointment to look in the mirror each day, but it also can be downright painful as our joints begin to deteriorate.

More than 700,000 knee replacements and 330,000 hip replacements are performed each year in the United States. With an aging population and obesity on the rise, demand for total knee and hip replacement surgery is expected to exceed 4 million by 2030.

So, can anything be done to reverse this trend? A UNMC developmental biologist, Andrew Dudley, Ph.D., and a University of Nebraska-Lincoln engineer, Angela Pannier, Ph.D., are taking a stab at it. The unlikely duo are seeking a mechanism for repairing and regenerating cartilage, the tissue between joints that prevents the bones from rubbing against each other.

The theory is simple. If you can repair or regenerate the cartilage, it would go a long way toward reducing the need to have total joint replacement surgery.

Of course, some things are easier said than done. “Cartilage is unique,” Dr. Pannier said. “It doesn’t repair itself like most other tissues in the body. It’s similar to highway construction. You look for cracks and try to patch them, but once deterioration begins, it’s never the same.”

Dozens of labs around the country are working on cartilage regeneration. Most focus on the more straightforward approach of generating mature adult cartilage, Dr. Dudley said.

However, early attempts have found that the new cartilage is not near as strong as original cartilage. “Cartilage cells reside in a protein/sugar scaffold that changes over time and with use,” Dr. Dudley said. “In some ways, each of us contains customized cartilage.

“We have shown that it takes time for cartilage cells to build the scaffold in the laboratory and that maintaining healthy cartilage cells requires growth factors and physical contact with the scaffold during the first few days of culture.”

A second issue that needed to be addressed is that cartilage cells are exposed to different environments, Dr. Pannier said. Depending on where cells are located in the cartilage, they will see different levels of growth factors, nutrients and scaffold structure, she said. “Most laboratories are using uniform conditions to generate cartilage,” Dr. Pannier said. “We developed a novel approach to generate cultures composed of layers that contain different growth factors and/or scaffold structures that will allow us to fine-tune the culture conditions.”

By combining their skills in engineering and biology, Drs. Dudley and Pannier hope to mimic the cell and scaffold structure of young cartilage and allow this cartilage to mature within the patient.

It’s a more challenging way of generating new cartilage – and could take many years – but the two are convinced that it is the best method of attacking the problem.

“We speak two very different languages,” Dr. Dudley said. “Engineers want to produce something. Biologists want to learn something. But together we can accomplish something important.”
Saving the world starts in Nebraska.

The world may know UNMC for our expertise dealing with the Ebola virus. But from Falls City to Scottsbluff, the people of Nebraska know us as the champion of a healthy state. From addressing the state’s nursing shortage to training nearly half of Nebraska’s health professionals to – along with our clinical partner, Nebraska Medicine – pumping billions of dollars into the state’s economy each year, UNMC never stops working to make our great state even stronger. UNMC. Breakthroughs for life.®