UNMC’S 2011 SCIENTIST LAUREATE TACKLES PANCREATIC CANCER
BIODBANK IS INVESTMENT IN FUTURE TREATMENTS
UNMC soon will open a new type of bank—one that will advance medical treatments.

ON THE COVER:
Tony Hollingsworth, Ph.D., is the 2011 Scientist Laureate, the highest honor given to a UNMC researcher.

RESEARCH IRONMAN TACKLES PANCREATIC CANCER
UNMC’s new Scientist Laureate wants to find new diagnostics and therapies for pancreatic cancer, a disease in which the lifetime risk of developing is one out of 79 people.
In a breakthrough technique, a combination of microbubbles and guided three-dimensional ultrasound impulses are used to dissolve blood clots in children.

Genetically altered mice that mimic human diseases have revolutionized medical research.

Pancreatic cancer is relentless, but four of UNMC’s scientists are working to find ways to treat this deadly disease.

A UNMC nurse-led project aims to reduce cases of post-operative delirium.

Researchers examine the cause of lung disease that plagues workers in hog farms and other agricultural settings.
RESEARCH TEAMS IMPACT HEALTH CARE

Every spring UNMC highlights some of its top scientists at the Distinguished Scientist Award ceremony (read more about them in this issue).

Awards are given to early career investigators who have received their first independent funding, established investigators who are named Distinguished Scientists, and one investigator who receives the Scientist Laureate Award.

This last award is the highest award given to a researcher at UNMC. To qualify he or she must be a UNMC faculty member for at least five years, have a clear track record of significant funding and a portfolio of highly cited publications, as well as being a nationally recognized research leader. Dr. Tony Hollingsworth, well known in pancreatic cancer research, has been named this year’s Scientist Laureate.

New among the Distinguished Scientists this year are researchers who are critical to many research teams. These collaborating scientists are often not the lead researcher, but because of their special expertise, are essential to, and collaborate with, many teams.

Increasingly, it is the case that one researcher does not have all the skills needed to solve complex research problems. Teams of researchers are important not only to finding the answers to complex problems, but also to move the research along more quickly.

Research collaborations occur at all levels — local, regional, national and even global. For example, in this issue you will meet Dr. Michele Balas who works with a team of clinicians and intensive care personnel to help her identify and recruit patients for her delirium study.

Dr. Matthew Zimmerman studies the role of the brain in the pathogenesis of hypertension and brings together scientists around the topic of antioxidant research to develop tools to share and learn from one another. Dr. Risto Rautiainen leads a center grant, which provides new opportunities for faculty focused on agricultural safety and health to connect across multiple states, including the project focused on the impact of hog dust. Finally, Dr. Surinder Batra leads a grant where four UNMC investigators form a local team that also is part of a network of scientists across the country attacking pancreatic cancer.

As these teams and collaborations show, UNMC is not only focused on improving health care in Nebraska but also is directly impacting research and health care beyond Nebraska.

Jennifer Larsen, M.D.
UNMC Vice Chancellor for Research
Security will be tight at the new bank opening on the UNMC campus. Patients at The Nebraska Medical Center will make deposits voluntarily. Scientists will make withdrawals. Together, they hope the biobank — a large, broad-based collection of biologic samples — will more quickly move breakthroughs in the laboratory into advances in the clinic that can improve the health of Nebraskans.

That would be the greatest return on investment.

The biobank, expected to open by December, will be a tremendous resource for UNMC’s scientists, said Jennifer Larsen, M.D., vice chancellor for research.

DNA and serum withdrawn from the biobank will enable scientists to bridge research between animal models and clinical trials.

“It can serve as preliminary evidence for funding requests for new areas of clinical research and clinical trials,” Dr. Larsen said.

It also can tell the scientists themselves if they are on the right track. UNMC already has multiple, condition-specific biobanks with samples from people who have consented to help with a certain area of study.

But, the need for a larger resource is vital, Dr. Larsen said, noting the dilemma faced by UNMC’s pancreatic cancer team.

“For five years, they’ve tried to recruit individuals who may be at risk for pancreatic cancer to test new biomarkers of risk and they still haven’t gotten the number of samples they need,” she said.

UNMC’s new biobank could allow multiple investigators to more quickly test these new markers of disease in people with, and without, a particular disease.

Everyone treated at The Nebraska Medical Center and UNMC clinics will have the opportunity to donate leftover blood from blood tests for research instead of having it discarded. Personal information will be removed to protect the confidentiality of the donor. A peer-review committee will monitor the materials’ use.

The project, funded by the Nebraska Research Initiative and UNMC, is being developed with staff and expertise from the Clinical Research Center at The Nebraska Medical Center and UNMC scientists from genomics, bioinformatics and various clinical labs.

Children’s Hospital & Medical Center also is interested in the project and is considering being a part of it, Dr. Larsen said.

UNMC’s biobank will be a key cog in UNMC’s translational research, Dr. Larsen said: “So we spend more time working on things that matter.”

by Kalani Simpson
Clinical trials may help defuse a time bomb

Timothy Baxter, M.D., has worked on aortic aneurysms since he came to UNMC in 1990.

Now, his investigation into a potential non-invasive treatment for abdominal aortic aneurysm has resulted in a $9.2 million grant from the National Institutes of Health to conduct a multi-center trial.

Animal models have shown the drug doxycycline could slow an aneurysm’s growth, to the point that it may never end up big — or dangerous — enough to require surgery.

That’s important for patients, who are told they have an aortic aneurysm — but that it might take five to 10 years for the aneurysm to reach operable size.

Dr. Baxter, a professor of surgery, has compared his patients’ anticipation to listening to a time bomb tick.

But doxycycline targets the proteins that break down tissue and allows the aorta to expand out.

The treatment would be non-invasive and proactive — and give patients peace of mind that something was being done.

UNMC will serve as the clinical coordinating center for a 16-site, triple-blind study enrolling 248 patients.

Dr. Baxter and UNMC did much of the preliminary work, but teamed up with three other respected co-investigators and their institutions to bring the NIH grant to fruition. The University of Maryland added much-needed expertise in clinical trial development and design. The University of Wisconsin will host the imaging core. And Washington University of St. Louis, which will host the biomarker core, was the first to show how to block the forming of aneurysms in mice.

UNMC HIV study deemed Science journal’s scientific breakthrough of 2011

UNMC physician/researcher, Susan Swindells, M.B.B.S., was a co-investigator for a study that Science, the country’s leading science journal, has deemed the scientific “Breakthrough of the Year.” The researchers say it could lead to the end of the HIV/AIDS epidemic.

The 2011 study showed that the use of a combination of antiretroviral drugs by those with HIV/AIDS could stop the transmission of the disease to others in 96 percent of cases.

“This is a game changer in that it really works,” said Dr. Swindells, the Terry K. Watanabe Professor and medical director of the HIV Clinic at UNMC. “What it means is that we could potentially treat our way out of the epidemic.”

The use of the medications can essentially quarantine the virus in those who already have it, Dr. Swindells said, which could halt its spread and lead to its complete eradication.

Major challenges exist, particularly when it comes to the distribution of the medications, said Dr. Swindells, who noted that nearly 40 million people are infected with HIV and less than half of them have access to the drugs.

But the therapy’s effectiveness in the study has shifted the conversation about AIDS on many fronts. The study was even referenced by President Barack Obama earlier this year as he pledged more U.S. support to fight AIDS.

“To truly implement this treatment will take tremendous political will and financial support and it remains to be seen if that will manifest,” Dr. Swindells said. “But if it does, it could mark the end of AIDS, and that’s an amazing thought.”

Research rises in U.S. News rankings

UNMC’s research enterprise rose four spots to tie for No. 62 in the 2013 U.S. News & World Report rankings of the top graduate schools.

Research joins primary care, which rose to No. 6, and rural health, which rose to No. 12, as UNMC programs that have ascended for two consecutive years in the rankings.

All three rankings — research, primary care and rural health — were based on a survey of 149 U.S. medical schools.

Other programs that were newly ranked this year were:

- The College of Pharmacy — 32nd out of 125 U.S. schools of pharmacy; and
- The School of Allied Health Professions’ physical therapy program — 34th out of 201 U.S. PT programs.

“Our continued ascension in these areas — which are vital to UNMC’s mission — is great news for the entire state of Nebraska,” said UNMC Chancellor Harold M. Maurer, M.D.
Breast cancer discovery pushes science forward

Every three minutes a woman in the United States is diagnosed with breast cancer. Of these, approximately one in five test positive for Her2, an aggressive type of cancer that is less responsive to hormonal therapy.

Now, thanks to a UNMC scientist, strides are being made in dealing with Her2.

While trying to recreate the findings of a previous study to determine therapeutic relevance, Kay-Uwe Wagner, Ph.D., and his former graduate student Qian Zhang, Ph.D., discovered something unexpected.

“It was always thought that by inhibiting a certain protein, Cyclin D1, the growth of breast cancer cells could be stopped or at least slowed,” said Dr. Wagner, professor in the UNMC Eppley Cancer Center.

Instead, he found the opposite to be true. In collaboration with Hallgeir Rui, M.D., at the Kimmel Cancer Center in Philadelphia, Dr. Wagner’s team discovered that even though a significant subset of breast cancers produce Cyclin D1, the more deadly Her2-positive cases produce more of a similar protein called Cyclin D3.

“Both proteins are known for turning normal cells into cancer cells,” he said.

The new research suggests that only the combined inhibition of both proteins might be enough to stop the uncontrolled growth of Her2-positive breast cancer cells.

“The next step will be to test drugs that can do precisely that,” Dr. Wagner said.

Dr. Wagner’s findings were published in the December issue of Cancer Research, one of the world’s most frequently cited cancer journals.

UNMC oncologist heads new guidelines panel

Pediatric oncologist Peter Coccia, M.D., Ittner professor and vice chairman of pediatrics, chaired a national panel that developed new guidelines for the diagnosis, treatment and after therapy of adolescents and young adults (AYA) with cancer.

AYA, comprised of 15- to 39-year-olds, represent a challenging age group for oncologists to treat successfully.

The guidelines were developed through the National Comprehensive Cancer Network® (NCCN®), an alliance of 21 of the world’s leading cancer centers. The UNMC Eppley Cancer Center is a charter member of the NCCN.

“Patients in this age group with pediatric types of cancers such as acute lymphoblastic leukemia and bone and soft tissue sarcomas have better outcomes when treated with aggressive therapies utilized by pediatric oncologists,” Dr. Coccia said.

Access the NCCN Guidelines for AYA Oncology at NCCN.org.

Dr. Kanmogne aims to improve AIDS care

In Cameroon, the high cost of antiretroviral medications to treat HIV/AIDS makes the drugs out of reach for most people.

Georgette Kanmogne, Ph.D., M.P.H., hopes her research on the neurological effects of HIV/AIDS enables health care providers to consider neurocognitive disorders caused by HIV when making treatment decisions.

And she has help through a five-year, $3.1 million grant from the National Institutes of Health (NIH) and the Fogarty International Center.

Dr. Kanmogne, associate professor and vice chairwoman for faculty development and resources allocation in the department of pharmacology and experimental neurosciences, studies the neurological impact of HIV/AIDS among the population in Cameroon and also in those with subtypes of the disease.

All three known strains of HIV and 11 subtypes of the virus are found in Cameroon.

The study will help determine whether particular genetic variants of the virus are more likely to cause neurological disorders and toxicity affecting morbidity and mortality.

Researcher lands $1.5 million grant to fight lupus

Lupus — one of the hardest chronic illnesses to diagnose — mimics diseases from fibromyalgia to diabetes. The debilitating autoimmune disease can lead to fatal organ damage.

“It’s a difficult, but fascinating disease,” said Kaihong Su, Ph.D., assistant professor of pathology and microbiology and principal investigator on a $1.5 million National Institutes of Health grant to study how the disease progresses and identify biomarkers that signal organ damage.

The five-year grant involves 11 UNMC clinicians and researchers and more than 50 patients.

Lupus turns the body’s greatest defense, the human immune system, against itself causing painful symptoms, Dr. Su said.

Since lupus is incurable, symptom management becomes the top priority. In time though, the disease progresses and the immune system begins to attack internal organs. Dr. Su’s top priority is to predict when the disease has progressed to this point.
No challenge is too big for Tony Hollingsworth, Ph.D.

That’s why this Ironman, who has completed 2.4-mile swims, 112-mile bike rides, and 26.2-mile runs, has spent the past 20 years focused on one of medicine’s most lethal diseases — pancreatic cancer.

“I chose pancreatic cancer because it was a big problem and no one else wanted to do it,” he said.

Today, the internationally renowned professor and director of pancreatic cancer research at the Eppley Institute studies the biology of pancreatic tumor progression in an effort to find new diagnostic and therapies for a disease in which the lifetime risk of developing is one out of 79 people.

“Dr. Hollingsworth has been at the forefront of his field for many years and is an international figure in the world of pancreatic cancer research,” said Jennifer Larsen, M.D., vice chancellor for research. “His work provides hope to those who are faced with one of the most lethal diseases known to mankind.”

Now, he has been named the 2011 Scientist Laureate, the highest honor given to a UNMC researcher. He was named a Distinguished Scientist in 2006 and 2010.

Dr. Hollingsworth appreciates the recognition, but is happiest focused on the challenge. He is principal investigator of a $5.3 million, five-year Specialized Program of Research Excellence (SPORE) grant in pancreatic cancer and leads a Biomarker Discovery Laboratory that is part of the Early Detection Research Network of the National Cancer Institute.

He also is quick to say the Scientist Laureate Award is about his team — the students, postdocs and technicians. “I’ve always said 15 to 20 minds are better than one, so my principal responsibility is to create an environment where people can be creative, think and undertake experiments to test their ideas.”

Those minds — along with a legion of clinicians, pathologists and research colleagues — explore the biology of pancreatic tumor progression from early lesions to metastatic disease. The medical center’s organ harvest/rapid autopsy program — one of few in the country — enables patients who die with pancreatic cancer to donate their organs for research purposes.

Their generosity — to fight cancer after death — is immeasurable in helping UNMC’s pancreatic team advance knowledge of the disease. “Pancreatic cancer kills because it spreads rapidly from a primary tumor to many other sites,” Dr. Hollingsworth said. “We don’t normally get access to these tissues so this gives us an opportunity to capture the entire history of the disease progression. We can examine the tumor and study exactly what has happened during its spread.”

Since the program started five years ago, the pancreatic team has studied the disease progression of more than 50 people and
received funds to study critical questions that could help future patients. Once diagnosed, a person has less than a 5 percent chance of living more than five years.

New genomic technology, along with the human specimens, enables Dr. Hollingsworth’s team to study issues few others can address: the molecular history of disease progression during lymphatic invasion and metastasis to lymph nodes.

Perineural invasion, too, is an area of interest. “We want to understand how tumors interact with nerves, metastasize along nerves, and cause pain,” he said. The group will study that by dissecting tumor cells and profiling their RNA expression to glean ideas on how to block the perineural invasion process therapeutically. He also wants to develop diagnostic methods to help clinicians know if a tumor has spread.

“We want to provide a better quality of life and extend survival,” he said. “More than that, if we understand the biology of how tumors spread and affect the functions of different organ systems, we should be able to design therapies to stop the process or better treat the systemic problems caused by tumors.”

Dr. Hollingsworth also continues to study MUC1, a complex mucin-like glycoprotein, which likely plays a role in regulating metastatic processes.

The Ft. Lauderdale, Fla., native has always looked at life analytically and says, “I was born to be a scientist.”

His parents — an insurance salesman and nurse — taught him to work hard, be persistent and not be easily defeated. Another lesson came from the high school football field, where he played offensive line. “That’s my approach to life and science,” he said. “I don’t mind doing the nitty-gritty work that might provide an opening to let someone else go for a big run.”

His lab, too, is filled with scientifically creative and fearless minds. Failure is OK, he tells them, because it provides new insights and perspectives into a disease that, as a result, is far better understood today than when he joined UNMC in 1991.

“It’s like an Ironman. If you looked at the whole challenge in one glance, you’d never even start. You have to take that first step, keep advancing and, once you’re well into the course, look back and realize ‘that was significant.’ I’ve never had any doubt that this is what I should be doing.”
Ask a scientist at UNMC what they like about their job and most will say, “I like to find out why things work.”

Why do cells act like they do? Why do genes malfunction? Why do diseased cells develop resistance to treatment?

An infinite number of questions begin with “Why,” followed by an infinite more that start with “What if?”

These questions lie at the center of every researcher’s soul. At UNMC, 22 of the very best were recognized as Distinguished Scientists and New Investigator award winners for 2011.

The researchers study some of the world’s most complex health issues from cancers to infectious diseases to minimally invasive surgery to HIV/AIDS.

Now in its sixth year, the chancellor-sponsored awards recognize UNMC researchers who have been among the most productive scientists in the country over the past five years. Each are recognized leaders in their field and, this year, represent the UNMC Colleges of Dentistry, Medicine, Nursing, Pharmacy, Public Health, the Munroe-Meyer Institute and the Eppley Institute for Cancer Research.

Distinguished Scientist recipients must lead an outstanding research program, publish research results in journals of the highest quality and show an ability to attract and retain extramural funding.

New Investigator Awards go to outstanding UNMC scientists who, in the past one to three years, have secured their first funding from the National Institutes of Health, the Department of Defense or other federal sources. New Investigators also must demonstrate scholarly activity such as publishing their research and/or presenting their findings at national conventions.

Distinguished Scientists and New Investigators receive merit-based salary supplements of $10,000. As Scientist Laureate, Tony Hollingsworth, Ph.D., director of Pancreatic Cancer Research, Eppley Institute, received a $20,000 supplement.

Named a Distinguished Scientist in 2006 and 2010, Dr. Hollingsworth studies the biology of pancreatic tumor progression in an effort to find new diagnostics and therapies for the deadly disease.

2011 Scientist Laureate Tony Hollingsworth, Ph.D.

2011 New Investigator Award Winners

- **Gregory Oakley, Ph.D.**
  College of Dentistry
  Cancer biology

- **Mayumi Naramura, M.D.**
  Eppley Institute
  Breast cancer

- **Maneesh Jain, Ph.D.**
  College of Medicine
  Pancreatic cancer

- **Tricia LeVan, Ph.D.**
  College of Medicine
  Chronic Obstructive Pulmonary Disease

- **Eyal Margalit, M.D., Ph.D.**
  College of Medicine
  Age-related macular degeneration
2011 Distinguished Scientist Award Winners

Michael Boska, Ph.D.
College of Medicine
Bioimaging

Paweł Ciborowski, Ph.D.
College of Medicine
Neurodegeneration

Georgette Kannmogne, Ph.D., M.P.H.
College of Medicine
HIV

Guangshun Wang, Ph.D.
College of Medicine
Antibiotic resistance

Michele Balas, Ph.D.
College of Nursing
Delirium and critical care

Preethy Nayar, Ph.D.
College of Public Health
Hospital efficiency and quality

Jill Poole, M.D.
College of Medicine
Respiratory disease/farming

Pawel Ciborowski, Ph.D.
College of Medicine
Neurodegeneration

Marlene Cohen, Ph.D.
College of Nursing
Palliative care

Debra Romberger, M.D.*
College of Medicine
Respiratory disease/farming

Paul Sorgen, Ph.D.*
College of Medicine
Ischemia-induced cardiac arrhythmias

Wayne Fisher, Ph.D.
Munroe-Meyer Institute
Autism

Tatiana Bronich, Ph.D.*
College of Pharmacy
Drug delivery in cancer

Todd Wyatt, Ph.D.*
College of Public Health
Lung disease

Dmitry Oleynikov, M.D.
College of Medicine
Robotic and minimally invasive surgery

Iraklis Pipinos, M.D., Ph.D.
College of Medicine
Blood vessel disease

Jane Meza, Ph.D.
College of Public Health
Biostatistics

Michael Boska, Ph.D.
College of Medicine
Bioimaging

Marlene Cohen, Ph.D.
College of Nursing
Palliative care

Wayne Fisher, Ph.D.
Munroe-Meyer Institute
Autism

Debra Romberger, M.D.*
College of Medicine
Respiratory disease/farming

Paul Sorgen, Ph.D.*
College of Medicine
Ischemia-induced cardiac arrhythmias

Todd Wyatt, Ph.D.*
College of Public Health
Lung disease

* denotes two-time Distinguished Scientists

View photos from the Distinguished Scientists Award Ceremony.
Read profiles of Distinguished Scientists and New Investigators.
unmc.edu/discover
Busting clots in children’s blood vessels

by Kalani Simpson

Shelby Kutty, M.D., applies ultrasound and microbubble treatment to an arterio-venous shunt placed in a pig.
Children who have cancer or other conditions that require long-term catheters, shunts or tubes are always in danger of developing blood clots. And that can lead to stroke.

Shelby Kutty, M.D., assistant professor of pediatric cardiology, wants to non-invasively blast those clots apart layer by layer, “like peeling an onion.”

Dr. Kutty investigates how microbubbles and guided three-dimensional ultrasound impulses can dissolve blood clots in children, while 3-D ultrasound imaging shows the process in real time.

This breakthrough technique has earned Dr. Kutty early career investigator awards and grants from the American Society of Echocardiography, the American College of Cardiology and the American Heart Association.

Tom Porter, M.D., professor of cardiology at UNMC, perfected the technique in adults and has mentored Dr. Kutty with this new application. “His work in pediatrics is unique,” Dr. Porter said. “No one else is doing this anywhere in the world right now.”

Dr. Kutty also wants to use the technology to prevent the clotting off of grafts and shunts in kidney and cancer patients. And he’s collaborating with Dr. Porter and Irving H. Zucker, Ph.D., professor and chairman, cellular/integrative physiology, to investigate the use of microbubbles and ultrasound to break up abnormal growth to treat infections in the heart.

The group also is investigating the success of this treatment to relieve groin artery spasm and improve blood flow after heart catheterization.

All of the projects are at the animal model stage, but clinical trials for the pediatric project may be just two years away.

“This would be a huge breakthrough because the clot-busting drugs we use on adults can cause torrential bleeding in children,” Dr. Kutty said.

“Kids need their own therapies,” he said. “They’re not just little big people.”
Only 1 percent of human genes lack counterparts in mice, which is what makes the mouse such a great model to study human diseases.

While 99 percent of genes in humans have counterparts in the mouse, 80 percent have identical, one-to-one equivalents.

The similarities are what provide researchers fertile ground in which to create medical breakthroughs. Tens of thousands of human and veterinary medicines in the market today are the results of research using laboratory animals, particularly the mouse.

Since 1 percent of human genes have no mouse counterparts, some human diseases cannot be tested in them, unless the mouse is specially designed to carry human blood and cells.

“Mice are always teaching us,” said Larisa Poluektova, M.D., Ph.D., associate professor of pharmacology and experimental neuroscience, who adapted a specially-designed mouse model for HIV dementia research.

Because mice cannot acquire HIV, UNMC has developed mice with the equivalent of a human immune system that can now “catch” HIV. Such a mouse model enables advanced tests on HIV and its treatment.

“Some things are specifically human and only human. That’s why we were so excited to develop this special mouse,” she said.

She and Santhi Gorantla, Ph.D., assistant professor of pharmacology and experimental neuroscience, and their team were the first to describe the development of changes in the brains of these mice.

Approximately 95 percent of all lab animals are mice and rats. In the past decade, scientists have discovered how to breed mice with genetic alterations that mimic human diseases. This capability has revolutionized medical research and dramatically increased the number of mice used in medical science.

Two types of mice — knockout and transgenic — dominate the research arena. A knockout mouse is genetically engineered to have an inactivated, or “knocked out,” gene that is replaced or disrupted with an artificial piece of DNA. By causing a specific gene to be inactive in the mouse, and observing any differences from normal behavior or physiology, researchers can infer its probable function.

A transgenic mouse contains additional, artificially-introduced genetic material in every
cell and is used to study gene function and regulation because analysis is carried out on the whole organism. Transgenic mice also are used to model human diseases that involve the overexpression or misexpression of a particular protein.

C.B. Gurumurthy, Ph.D., assistant professor of genetics, cell biology and anatomy, directs the UNMC Mouse Genome Engineering Core Facility, funded by the Nebraska Research Initiative and tobacco settlement funds. Since he took this position nearly two years ago, he has become the “mouse guru” to whom researchers turn for advice about mouse models.

“Genes are like stars in the sky — what happens to the rest of the universe when we take out one star?” Dr. Gurumurthy asked.

“That is a question many researchers want to answer. We help researchers create designer mice that could enable them to get to the answer. We take out the star of their interest from the mouse genome universe or insert an artificial star into it.”

Dr. Gurumurthy constantly looks out for newer trends in transgenic technology. One of the biggest drawbacks of the existing transgenic technology is the randomness of gene integration into the genome.

“It is like when you insert a star into the genome universe and it gets lost somewhere,” he said.

But now, a gene can be placed in the mouse genome at a precise location using a novel technique called PITT (Pronuclear Injection-based Targeted Transgenesis). He collaborates with a Japanese group to try this technique at UNMC. The technology could save researchers up to two years and $25,000 in screening each mouse line to determine if it is useful.

He uses a system that cuts in half the time it takes for researchers to change the genetic background of their genetically engineered mouse strain. It normally takes three years of “congenic breeding” to get the desired mouse, but with the “marker assisted speed congenics,” the time is reduced to about a year and a half.

“Just a handful of other labs in the United States, including only one other core lab, offer services using processes similar to ours,” Dr. Gurumurthy said. “The method, not readily available, is up to three times less expensive than a newer method that is used at some core facilities and commercial sources.”

He also has developed a genetically engineered fluorescent mouse model that illuminates individual cells that comprise various organs in the animal body. Called the “rainbow mouse,” Dr. Gurumurthy said it enables researchers to observe cellular interactions and organization during a disease process in real time.

“With this mouse model, researchers could watch how cancer grows and metastasizes to other organs in the body,” he said.

“Researchers could test new medications or use the rainbow mouse for developmental studies. It’s really quite extraordinary.”

How mice advance medical research

Breast cancer researcher Kay-Uwe Wagner, Ph.D., has worked with genetically engineered mice since 1995. Over the past decade, he has developed more than 20 mouse models that are now being used in cancer research around the world. Read more about how he and other UNMC researchers use mice to advance medical research.
FOUR SCIENTISTS TEAM UP TO INVESTIGATE PANCREATIC CANCER

We call them investigators because they solve mysteries. And four of UNMC’s top Sherlocks are on the case.

But this one isn’t a whodunit. We know the villain is pancreatic cancer. We know what it does — it kills.

It killed good-guy actor Patrick Swayze. It killed Apple inventor Steve Jobs. It killed scientist Ralph Steinman, M.D., just days before he would have heard he had won the Nobel Prize.

Maybe it’s taken someone you know, too. It has nearly 100 percent mortality rate once diagnosed.

The mystery is why it’s so lethal. The mystery is in what can be done to keep it from killing again.

Pancreatic cancer is relentless. Other cancers can sometimes be treated. But it seems no matter the treatment, the pancreatic kind always finds another way to spread.

“The drugs we now use don’t work well and patients have poor survival (less than 4 percent over five years),” said Surinder Batra, Ph.D.

Dr. Batra, professor and chairman, biochemistry and molecular biology, leads a team of four of UNMC’s best detectives — the Pancreatic Tumor Microenvironment Network (TMEN). The TMEN team works furiously, fueled by a $4.2 million grant from the National Cancer Institute. Dr. Batra is the principal investigator, but the other three also are research superstars.

Tony Hollingsworth, Ph.D., professor and director of pancreatic cancer research at the Eppley Institute, was just named UNMC’s sixth Scientist Laureate. Keith Johnson, Ph.D., professor in the College of Dentistry, and Rakesh Singh, Ph.D., professor and director of the pathology and microbiology graduate program, join Dr. Batra as UNMC Distinguished Scientists.

And if the villain is relentless, so are UNMC’s men and women in white coats.
They investigate the microenvironment of the pancreas, like a crime scene. This is where the clues are. This is where they think the answers will come.

Dr. Batra said his research suggests the microenvironment itself might be a “partner in crime.”

The TMEN are a team. They share findings, goals, resources. But each of the four investigators also brings his own team, his own piece of the puzzle, his own strengths.

Dr. Johnson leads a team that studies the spread of pancreatic cancer — specifically, the role of cell adhesion molecules and connective-tissue stromal cells. Dr. Johnson and his team will delete the gene for a specific cell-to-cell adhesion molecule and study the results.

“By manipulating the expression of cell adhesion molecules in specific types of stromal cells we hope to better understand the process of metastasis and how to control it,” Dr. Johnson said.

Meanwhile, Dr. Singh leads a team that investigates the role of CXCR2, a molecule that drives tumor-associated inflammation.

Chronic inflammation can lead to tumorigenesis — the creation of cancer. Tumors themselves are inherently pro-inflammatory, and scientists believe white blood cells are critical to tumor maintenance and progression. “Molecules driving tumor-associated inflammation have considerable potential as therapeutic targets, yet this area remains relatively underexplored in pancreatic cancer,” Dr. Singh said.

Dr. Hollingsworth’s team examines lymphatic invasion — how cancer attacks nearby lymph nodes — and metastasis. He continues to investigate the role of Sonic Hedgehog, a signaling protein, in this scenario. His project also uses laser capture microdissection and Ribonucleic acid sequencing of matched tissue samples from multiple patients with pancreatic cancer in order to search for further hypotheses.

Dr. Batra’s team studies the interplay of tumor microenvironment and MUC4. MUC4 mucin, a cell-signaling protein, is abnormally overexpressed in pancreatic cancer. Its overexpression also is associated with poor prognosis. Dr. Batra’s team investigates how MUC4 is regulated by the tumor microenvironment, and why cancer cells respond to cues by the microenvironment.

The goal of TMEN — the four investigators — is to go beyond basic science, to try to find something that will finally translate beyond the lab.

“Over the years, we’ve generated a lot of genetic information in animal models. Did we change the survival rate? No,” Dr. Batra said. “My question is why?”

Dr. Hollingsworth has said he works on this horrible disease because so few others do. Dr. Batra said, “I was fascinated by this chemical problem.” They’ve been a team, informally and otherwise, for more than two decades.

The four investigators have been working on pancreatic cancer together at UNMC for eight or nine years. But last fall, with the grant and the formation of TMEN, they made it official. They joined forces. And Kay-Uwe Wagner, Ph.D., professor at the Eppley Institute, joins them, to lead the TMEN genetically engineered model core. Some 12 faculty and 25 people work with them on this project in UNMC labs.

Part of pancreatic cancer’s deadliness is that it hides, waiting to strike. There are no screening tools and the location of the pancreas, deep in the abdomen, hinders early diagnosis. By the time most people know they have it, it’s already too late.

Pancreatic cancer is one of medicine’s deadliest mysteries. But there aren’t four other detectives you’d want on the case.
Alien abduction or delirium in the ICU?

UNMC nurse-led project aims to reduce cases of delirium in critical care units

by Kalani Simpson

From left: Brad Matthiessen, respiratory therapist; Dan Haskin, staff nurse; David Gannon, M.D., Keith Olsen, Pharm.D., Michele Balas, Ph.D., and Gregory Peitz, Pharm.D., model the kind of interdisciplinary communication needed to keep ICU delirium at bay.
For years, health care professionals believed that all measures taken in intensive care units (ICU) were for the patients’ own good.

Patients were tied down so they couldn’t pull out their lines or tubes. They were put on machines to help them breathe. Intravenous lines were inserted to deliver life-saving medications. Powerful drugs immobilized them.

The drugs gave patients the desired amnesia about the trauma they faced, but it also gave them something less desirable — delirium.

“As a nurse,” said Michele Balas, Ph.D., assistant professor in the UNMC College of Nursing, “I remember thinking, ‘I don’t want them to remember anything we’re doing to them.'”

But the drugs also contributed to something less desirable. Two-thirds of ICU patients show signs of “ICU delirium,” or acute confusion. “For years we thought that was just a normal condition, something that happens to all old people when they are in the ICU, and that they would get better before they went home,” Dr. Balas said.

“But in the past decade we have found that we’ve been so wrong.”

While the ICU keeps patients alive, it turns out the delirium can have lasting, even deadly effects. It is an independent predictor of higher mortality. Delirium often causes a loss of functional and cognitive ability such as an inability to balance the checkbook or help kids with homework. And older adults are more likely to go straight from the ICU into nursing homes or other long-term care facilities.

Up to 80 percent of people who are put on ventilators in ICU will experience delirium, Dr. Balas said.

“You never go home quite the same as when you went in.”

Though all of these measures are done with the best of intentions, the long periods of immobility and ensuing muscle atrophy, along with the drugs, not only erase memory, but also distort reality.

Studies have shown between 15 percent and 40 percent of ICU patients face symptoms of post-traumatic stress disorder.

Except the people Dr. Balas calls “ICU survivors” often don’t fully remember their traumatic experiences. They’re not sure if they really lived through them or not. They don’t know why they suffer from depression, anxiety, delirium and the rest. They don’t know why their brains don’t work the way they did before.

Some are left with emotional triggers, repressed memories, horrific flashback fantasies that rival an alien abduction, paranoid nightmares from somewhere out of a doped-up benzodiazepine fog.

“They think they’re crazy,” Dr. Balas said. They’re embarrassed to talk about it.”

But Dr. Balas is talking about it. In fact, she’s all but shouting that something needs to change.

The goal is, for a little while each day, to let patients wake up, get them off the drugs, take off the ventilators to let them breathe on their own, get them up and moving, and look closely for signs of delirium to address it in the early stages.

Evidence has shown that patients who breathe a little on their own each day are off the ventilator more quickly, Dr. Balas said.

Those able to touch base with reality every 24 hours are less likely to slip away, she said.

But it won’t be easy. The ‘C’ — coordination — is key. It takes an interdisciplinary team effort — all members must talk to each other and appraise the patient’s condition beyond meds and vital signs.

“The problem is changing the culture,” Dr. Balas said. She admits it herself: “Patients are much easier to take care of when they’re down.”

But we never fully realized, until lately, all that was really going on, while they were down.

Part of the project will be building a website, which will be the first step toward establishing a national support network for ICU survivors, Dr. Balas said.

UNMC and its hospital partner, The Nebraska Medical Center, are the first in the country to concurrently try every element of ABCDE to see if it will help patients. And yes, Dr. Balas said, doing it this way is going to be a lot more work.

“We’re asking a lot of our nurses,” Dr. Balas said. “But, if it helps to stop a nightmare, it’s worth the extra effort.”

Read a first-hand account of one woman’s ICU experience. See how imagery has helped her process her experiences.
They eat, drink and poop, and when hundreds are confined in a closed hog facility the dust that’s stirred up contains bacteria that cause lung disease in farm workers.

Physicians report an increase in upper and lower respiratory problems among farm workers, who might spend all day in the loud and dusty confinement facilities. It’s estimated that more than one-third of those who work in swine and dairy facilities develop lung disease related to dust exposure.

Nebraska is the No. 1 producer of cattle and calves and No. 3 in hogs and pigs in the United States. As the global demand for meat increases, animal production is likely to flourish in the state.

To help farm workers stay healthy, UNMC’s Central States Center for Agricultural Safety and Health (CS-CASH) is investigating the fundamental mechanics of chronic inflammatory lung disease associated with inhalation of organic dust.

“We want to understand what happens to the lungs of workers as the industry changes and more people are exposed to organic dusts for longer periods of time,” said Todd Wyatt, Ph.D., professor of environmental, agriculture and occupational health in the College of Public Health.

As part of the Ag Center, he and allergist Jill Poole, M.D., associate professor, are investigators of a $750,000 grant from the National Institute for Occupational Safety and Health in the Centers for Disease Control and Prevention (CDC). Deb Romberger, M.D., professor, pulmonary, will conduct outreach activities to help prevent farmers from getting respiratory disease. This is one of six projects funded through the newly established CS-CASH. (See story page 21.)

Dr. Poole, who treats many farmers for such respiratory problems as chronic bronchitis, asthma and chronic obstructive pulmonary disease (COPD), said there are no medications on the market that work well.

“We struggle to control the symptoms. That’s why this study is so important.”

Drs. Wyatt and Poole test the effects of Gram-negative bacteria, which have an established role in respiratory disease, and also have branched into a new area — Gram-positive bacteria.

“Each bacterium can stimulate the immune system differently,” Dr. Poole said. “If
we understand the difference it will give us better ideas where to target therapy.”

The researchers have expanded their investigation to include the “big picture” of multiple exposures, or what Dr. Wyatt calls the “triple whammy” — smoking, alcohol and dust.

In deaths caused by lung disease, tobacco smoking is No. 1, causing nearly 85 percent of all deaths; obesity is a distant second and alcohol is third.

COPD now follows heart disease and cancer as the third most deadly disease in the world. By 2030, the American Thoracic Society expects it to claim the top spot.

“Multiple exposures are possibly the bigger problem,” Dr. Wyatt said. “We have an innate defense system in the lungs in which inhaled viruses, bacteria, and other particles are effectively removed through the action of mucociliary clearance. Throw in cigarette smoke or alcohol exposure and the lung’s normal defense system is severely compromised.”

Add the complexity of individual genetics — why two people exposed to similar environments react differently — and researchers are left with multiple variables.

The lungs efficiently respond to inhaled substances, but when exposure is continuous, the level of inflammation can lead to injury.

“If the body continuously responds to inflammation, it begins a cascade of responses that overwhelm the system and can lead to additional prolonged damage,” Dr. Wyatt said.

To find the cellular mechanisms during inflammation, the research team uses knockout mouse models to learn what happens to specific proteins, such as Toll-like receptors, and the cell signaling pathways when a liquid extract of the dust is inhaled.

About UNMC’s Ag Center

How bacteria in hog dust triggers respiratory disease is one of six projects funded through UNMC’s Central States Center for Agricultural Safety and Health (CS-CASH), directed by Risto Rautiainen, Ph.D., associate professor of environmental, agricultural and occupational health.

It is one of nine regional centers funded by a five-year, $5.25 million grant from the National Institute for Occupational Safety and Health in the Centers for Disease Control and Prevention.

The key projects for the center include research on asthma, agricultural injury surveillance, hearing protection use, National Ag Safety Database, health and safety education of farmers and outreach.

During the past 10 years, agriculture has outpaced mining as the most hazardous industry in the nation, based on occupational fatality rates. Farm machinery, animals and falls are the top three causes of death on the farm.

“Personal protection often takes a back seat to production on the farm,” Dr. Rautiainen said. “If we can prevent or control respiratory disease, then farmers can stay in business that much longer.”

Covering seven states in the Midwest, the new center serves not only Nebraska, but nearly one quarter of American farmers.

The dust research at UNMC builds on what pulmonologist Susanna Von Essen, M.D., started 27 years ago.

She was part of the international group of scientists who coined the term “organic dust toxic syndrome,” a condition similar to the flu with headaches, muscle aches and fatigue occurring a few hours after working in a confinement building.

Dr. Von Essen, professor of pulmonology and environmental, agricultural and occupational health science, noted in 2005 that 13 percent to 20 percent of workers exposed to swine confinement barns reported chronic bronchitis symptoms.

It was her dedication to the health and safety of Nebraska’s farmers that eventually led to the establishment of the C-S-CASH, Dr. Rautiainen said.
Toll-like receptors are considered important therapeutic targets because they mediate initial immune responses and also are implicated in serious autoimmune diseases.

Another aspect of the project is how Vitamin D affects the Toll receptors. Dr. Poole is particularly interested in how nutrition and environmental exposures factor into the disease.

The CDC recommends farm workers wear a respirator facemask to filter airborne particles. On farms with more than 10 workers, the Occupational Safety and Health Administration respiratory program requires masks be worn if the dust level is higher than the permissible level. However, compliance on large and small farms is only 30 percent, at best, Dr. Poole said.

“We hope our research will lead to new treatments to reduce airway inflammation before it causes disease in workers.”

When clean is too clean

A little dirt never hurt, but today, people are fixated on staying super clean.

While a germ-free environment can prevent the spread of disease and infections, a super-clean lifestyle may be the cause for an increase of allergies among children.

The “hygiene hypothesis,” proposes that when the immune system is inadequately exposed to infectious organisms it becomes dysfunctional. The body’s immune system is designed to fight infection, but also recognizes foreign substances as allergens.

With the development of vaccines, the immune system no longer needs to fight off such life-threatening diseases as polio and measles. And thanks to antibiotics, the immune system is no longer burdened to the extent it was in the past, with fighting common bacterial infections.

The hygiene hypothesis intrigued UNMC allergist Jill Poole, M.D., who investigates how the immune system recognizes and responds to organic dust common to hog confinement buildings. The theory was first published in Europe, where researchers found lower rates of allergy and asthma among farmers.

“I thought it would hold true here too, but it’s not so in the United States. Although they have a lower rate of allergy, American farmers have a higher incidence of respiratory disease.”

The Financial Institution For Health Care Professionals

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Join your friends, become a Metro Credit Union Member/Owner today. Open a new checking account with Direct Deposit, and we’ll put $50.00 into your new account as our way of saying thanks.
Breaking the dysfunctional neuron cycle in hypertension

One out of every four adults is a walking time bomb. High blood pressure or hypertension runs in the blood vessels of 75 million people over the age of 20 and leads to heart disease, the main cause of death for men and women in the United States.

Called the silent killer, hypertension develops over many years with no symptoms. Only after a bodily organ is irritated or damaged are the consequences of high blood pressure realized.

Although there are several drugs to treat hypertension, 20 percent of people with this disease are resistant to current therapy. No matter what they do, their blood pressure stays high, putting them at risk for stroke or kidney disease.

“One of the greatest scientific challenges for the improved treatment of brain-related diseases, such as hypertension, is developing therapies that are able to penetrate neurons in the brain,” said Matthew Zimmerman, Ph.D.

Neurons form the basis of the central nervous system and communicate with the entire body through electrical and chemical signals.

Through a $1.2 million National Institutes of Health grant, Dr. Zimmerman studies a potentially new therapeutic target in the fight against hypertension and it involves the mitochondria of neurons.

Mitochondria, sometimes called cellular power plants, are a source of harmful superoxide radicals, which are produced when neurons are stimulated by angiotensin II (AngII).

“Their precise role, as it relates to the regulation of cardiovascular function and the pathogenesis of neurocardiovascular diseases, is unknown,” Dr. Zimmerman said.

In neurons, AngII increases superoxide, which in turn aids AngII-induced neuronal activation. Under normal circumstances, the brain also produces superoxide dismutase (SOD), an antioxidant enzyme that scavenges superoxide and keeps the levels of superoxide in check.

Trouble comes when AngII levels in the body are chronically elevated as this leads to more superoxide production and a system imbalance. Neurons are continuously activated and mobilize the sympathetic nervous system, which is known to play a key role in hypertension.

Knowing this, Dr. Zimmerman suspects that mitochondrial-produced superoxide also plays a key factor in regulating hypertension.

“We are trying to determine if targeting superoxide dismutase in the mitochondria of neurons could be a new therapeutic strategy for treating hypertension,” Dr. Zimmerman said.

While this focuses on the basics of intracellular signaling in-vitro, it compliments Dr. Zimmerman’s other, more translational, research. Dr. Zimmerman and collaborators in the Nebraska Center for Nanomedicine study a nanomedicine-based intervention for hypertension using a specially-designed nanozyme to deliver SOD protein to neurons.

Dr. Zimmerman hypothesizes that the SOD nanozyme enters neurons in regions of the brain that lack a blood-brain barrier (BBB). These BBB-deficient brain regions are known to control cardiovascular function. Increasing protein levels of SOD in these brain regions with the nanozyme will result in lower levels of superoxide and inhibition of AngII-induced neuronal activation.

Recent experiments show that a single injection of the SOD nanozyme inhibits AngII from increasing blood pressure, which could lead to a therapy in the future.

Originally from Wisconsin, Dr. Zimmerman was recruited from the University of Iowa, Iowa City, in 2007.

Postdoctoral fellows usually are recruited after they’ve done two- to five-years of research and acquired independent funding.

Dr. Zimmerman had barely two years of postdoctoral training and only fellowship funding when recruited by Irving H. Zucker, Ph.D., chairman of UNMC’s Cellular and Integrative Physiology Department.

“I had an intuition that Matt would do well and he hit the ground running,” he said.
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