UNMC sets the gold standard for Ebola care
This issue of UNMC Discover leads with several stories focused on the emerging threat of infectious diseases, such as Ebola and methicillin-resistant Staphylococcus aureus, and how UNMC is out front in the search for research strategies to prevent and treat them.

Behind these stories are two messages. First, biomedical research is directly linked to the needs of medical care. Health threats, from serious new infections and the obesity epidemic to shifts in frequency of diseases due to age or changing lifestyles, all drive the need for new research teams and strategies to address them.

For many diseases or problems, we often do not have a single solution for treatment or prevention. Ebola is one of those problems. This epidemic points out how important and how quickly new research can sometimes be required, whether it’s for day-to-day care, includes research nurses, pharmacists, contract specialists, human studies and other review committees.

With Ebola, as also the case in many cancers, we often need new therapies that dramatically change the course of the disease. And with new therapies, there is an often forgotten group of people, the volunteers who participate in clinical trials, who play a critical role as members of the team.

Other teams also are featured in this issue, including the important role mentors play in developing new investigators in large center grants and individual projects.

While it is still too early to discern the impact that the recent Ebola drugs may have, new investigational drugs and devices give us hope that the future of medicine will be better than today.

And this is why research is so important.

Jennifer Larsen, M.D.
UNMC Vice Chancellor for Research
UNMC sets the gold standard for Ebola care

Research leads to best practices in fight against highly infectious diseases

Lab testing for Ebola requires thinking ‘outside the box’

UNMC research team working on vaccine for Ebola virus

UNMC, Nebraska Medicine share Ebola expertise through online courses

Sticky cells are a sticky issue

Tight junctions and migrations of epithelial cells are under study in the College of Dentistry.

The scientist and his chicken soup

Every time cold season rolls around, so do home remedies, including Stephen Rennard, M.D., and his famous study of chicken soup.

How Ebola works

Get inside the killer virus and learn how it succeeds in disrupting the immune system.

COBREs build centers of excellence

Research centers of excellence develop with the help of grants from the National Institutes of Health.

Storm chaser to headline 2015 Nebraska Science Festival

Reed Timmer will kick off the biggest science festival in Nebraska in April.
The 2014 Ebola outbreak has been one of the most devastating public health crises in recent history. It’s an ever-evolving story that has stretched from West Africa to Omaha. The virus, which presents like malaria or flu in its early stages, initially caught health care professionals by surprise as it spread through eight West African countries. At press time, the death toll had reached more than 8,600, including nearly 350 health care workers.

In the United States, fear of the virus spread more easily than the virus itself and led to anxiety, false alarms, airport screenings and forced quarantines.

Cooler heads prevailed in Nebraska, however, where three patients were sent for treatment in September, October and November.

Two men, who contracted the virus in Liberia, were successfully treated and released at UNMC. A third, who had been in Sierra Leone and arrived in extremely critical condition, died despite heroic efforts to save him.

Why UNMC? UNMC has had a long-term focus on many infections, including dangerous emerging infections like Ebola. UNMC already is home to world-class research in HIV-AIDS, malaria and methicillin-resistant Staphylococcus aureus (MRSA).

The Nebraska Public Health Laboratory was developed on the UNMC campus in 1997 to provide the biosafety level 3 (BSL-3) laboratory necessary to not only test but do research on many highly contagious and pathogenic organisms as smallpox, anthrax, tularemia, avian influenza, Lyme disease, West Nile virus and Ebola. (See story page 7) In this facility, many infectious disease researchers are working on strategies for early diagnosis, vaccines, and other treatments for these diseases (See story page 8.)

The laboratory had been building and strengthening its expertise in emergency preparedness long before the 9/11 terrorist attacks on the United States. In 2005, UNMC developed the Nebraska Biocontainment Patient Care Unit as a collaborative project with the Nebraska Department of Health and Human Services and Nebraska Medicine to be prepared to care for individuals who have highly infectious diseases. The unit also has been proposed to the Department of Defense to be used to study new treatments for these diseases.

The largest of three biocontainment units that accept Ebola patients in the country, UNMC developed protocols that became the national standard for treatment thanks to the team’s experience in biopreparedness through quarterly drills conducted over many years. At times, Philip Smith, M.D., medical director of the Biocontainment Unit and professor of infectious diseases, felt pressed to justify the existence of the unit.

Each training drill, however, brought more refinements to the protocols – from personal protective equipment (PPE) and waste disposal to transportation and patient mental health.

With the arrival of Ebola patients, the protocols were implemented, but other opportunities and challenges arose.

There was a need to swiftly obtain and test new treatments. Chris Kratochvil, M.D., associate vice chancellor for research, worked collaboratively with Jon Beck, Pharm.D., nurse LuAnn Larson and Scott Koepsell, M.D., to obtain these treatments, sometimes from other countries.

They also had to develop protocols and obtain emergency permission to administer such drugs as ZMapp and TKM Ebola.

Partners in this process included UNMC’s Institutional Review Board, Emory University, the National Institutes of Health, the Food and Drug Administration and the White House.
Innovations in use of bedside diagnostics were developed by Steven Hinrichs, M.D., Stokes-Shackleford Professor of Pathology and Microbiology and department chairman; Pete Iwen, Ph.D., director of the Nebraska Public Health Laboratory (NPHL) and professor of pathology and microbiology at UNMC, and others.

Team members solved each of these issues with innovation and ingenuity.

UNMC’s innovations in transport, use of personal protective equipment, and waste disposal were not only extremely effective but caught the attention of the Centers for Disease Control and Prevention (CDC) and health organizations throughout the world. (See story below.)

Health teams have since turned to UNMC for best practices, which have become the gold standard in Ebola care, and UNMC has become one of two training sites for a larger number of designated hospitals helping the nation prepare to care for Ebola patients, if needed. (See story page 9.)

UNMC continues to work on new diagnostics, design of clinical trials that will be used in the U.S., as well as Africa, and how the genetics of the virus determines how it infects a person.

On another emergency preparedness front, UNMC researchers are helping to combat weapons of mass destruction as part of a collaboration between the University of Nebraska and the United States Strategic Command.

With the partnership, the University of Nebraska’s National Strategic Research Institute (NSRI), was established in the fall of 2012. The institute is one of 13 University-Affiliated Research Centers across the United States. NSRI focuses on five core research competencies in support of the United States Strategic Command, the Department of Defense and other agencies. (See story page 8.)

Recently, the World Health Organization asked UNMC to join its Global Outbreak Alert and Response Network (GOARN), a 300-plus worldwide network of institutions that react rapidly to outbreaks of international importance to cut response time to days and hours. These developments are part of a strategic plan designed to position UNMC and Nebraska Medicine as leaders in the field of biocontainment and emergency preparedness.

Research leads to best practices in fight against highly infectious diseases

Designed to handle everything from smallpox and SARS to avian influenza and Ebola, UNMC’s biocontainment unit is staffed by more than 40 highly trained professionals who have special training in disaster management, cardiac life support and bioterrorism.

They work full-time in other areas of UNMC’s primary clinical partner, Nebraska Medicine - but remain ready to report to the unit promptly. In the event of a public health threat, the Nebraska Department of Health and Human Services and the biocontainment unit’s medical director may activate the unit.

Almost as big as a basketball court, the 4,100-square-foot area on the seventh floor of University Tower is the largest of only three such units in the country specially equipped to handle an outbreak of this nature. The others are at Emory University in Atlanta and the National Institutes of Health in Bethesda, Md.

The five patient rooms in UNMC’s biocontainment unit are equipped with negative air pressure to handle airborne viruses (which Ebola is not), meaning that their exhaust fans pull in air and send it through HEPA filters with microscopic openings that trap the tiniest particles. The particles can’t leave the unit and infect areas outside.

Cheryl Rand, RN, (left) assists Jean Bellinghausen, respiratory therapist, on how a two-person team dons and dofs personal protective equipment. This is one of many best practices developed by UNMC’s biocontainment unit staff to be adopted as a national best practice.

This unit itself has become a laboratory for developing best practices of safety and treatment of patients with highly infectious diseases.

The donning and doffing of personal protective equipment (PPE), always a two-person effort in the biocontainment unit, has now been adopted as a gold standard, said Shelly Schwedhelm, executive director, emergency preparedness and infection prevention, Nebraska Medicine.

“One person follows the checklist, supervises and assists with the correct order of donning and doffing while a second person puts on the gear or carefully removes it with assistance as directed,” Schwedhelm said. “We found that this reduces the risk of exposure to potentially dangerous bodily fluids. It takes more time, but it’s safe.”
Other adjustments and improvements were made during and after the treatment of UNMC’s first Ebola patient, Rick Sacra, M.D., including:

- The five-room/10-bed unit became a two-room, two-bed unit when treating Ebola patients.
- The team switched to a new electronic stethoscope that provided better sound quality and reduced contamination risks.
- A mobile laboratory was moved into the unit to speed test results, allowing physicians to more quickly adjust a patient’s critical fluid and electrolyte levels. Before that, testing of specimens had been delayed for up to an hour because the main lab was across campus and required stringent and time consuming protocols to move the samples.
- Two rooms were converted into storage for extra equipment and used protective gear that was staged for the autoclave.

One of the key areas of concern related to the treatment of Ebola patients in the U.S. is waste removal. Ebola patients treated by the Nebraska team produced about 23 cubic feet – more than 50 pounds – of solid waste per day, most of which was PPE worn by health care workers.

UNMC’s experts in biocontainment patient transportation and waste management issues developed procedures to safely handle the waste. Shawn Gibbs, Ph.D., professor, and John Lowe, Ph.D., assistant professor, environmental, agricultural and occupational health, UNMC College of Public Health, worked with an autoclave in the UNMC Biocontainment unit to convert category A waste - waste known or expected to contain a deadly pathogen like Ebola - into category B medical waste to enable safe disposal. This innovation allows it to be shipped more safely and at a lower cost than category A waste.

While Ebola patients were in the unit, the autoclave operated for more than 12 hours a day.

Although the CDC allowed any patient-generated liquid waste to go down the drain and be treated by the municipal plant, prior research conducted by these two industrial hygienists led them to implement an inexpensive disinfectant route.

“We conducted risk assessments on every procedure and developed alternative scenarios in case things happened – a ‘what if?’ list,” Dr. Gibbs said.

Up to nine liters of liquid waste produced daily by Ebola patients was disposed into a toilet with hospital-grade disinfectant and held 2.5 times longer than the manufacturer recommended time before being flushed.

Because of these successful protocols and innovations, Nebraska Medicine and UNMC faculty and staff are working with the CDC and Emory University to provide training and educational resources to the staff at other U.S. hospitals that federal health officials recently designated as Ebola treatment centers, to increase the number of beds available to treat future patients.

“We conducted risk assessments on every procedure and developed alternative scenarios in case things happened – a ‘what if?’ list.”

Shawn Gibbs, Ph.D., professor
Lab testing for Ebola requires thinking ‘outside the box’

by Vicky Cerino

Professionals in laboratories across the UNMC campus are on the front line in helping physicians get the information they need to treat Ebola patients.

Pete Iwen, Ph.D., director of the Nebraska Public Health Laboratory (NPHL) and professor of pathology and microbiology at UNMC, and UNMC colleagues recently published an editorial in a top journal, the American Journal of Clinical Pathology. The paper provides guidance on the essential list of laboratory tests needed to support a patient infected with Ebola virus – and how to perform the tests safely.

This required professionals to think outside the box.

“We had to brainstorm to come up with alternatives,” said Dr. Iwen, first author of the editorial. “Some tests were requested that couldn’t be done safely with equipment available, so alternatives were developed. We had two goals in mind throughout to provide optimal testing and keep laboratory employees safe.”

He said their template of tests helps health professionals define what may be needed and how they can be run safely.

They turned to the journal so they could share the information with laboratories across the country seeking guidance.

“Normally it takes months to get a paper approved through the peer review process, additional months to get the galley proofs back with editing changes and potentially more months before it’s published,” Dr. Iwen said. “But in this case, it was fast-tracked.

“It took the editor of the journal about 18 hours to get the paper approved, which in my experience is unheard of. It was available electronically in about 10 days.”

Dr. Iwen said dealing with the Ebola virus in recent months has been like a whirlwind.

“We were prepared for the possibility that something like this could happen, but we were thinking more along the lines of pandemic flu,” Dr. Iwen said. “The technologists who work in the clinical laboratories on campus are a great group of professionals. They play a key role in providing safe testing and this leads to great care for patients every day,”

The NPHL biosafety level 3 (BSL3) became the first state public health laboratory in the U.S. to test specimens that were positive for the Ebola virus. It also was the first lab to commercially ship these specimens within the U.S.

“To me that’s a pretty big deal,” Dr. Iwen said. “When we called couriers, the phone went silent, followed by, ‘You want to do what?’ We had to educate the shippers on how they could handle our specimens while meeting federal guidelines. We even had the airlines calling us asking, ‘What’s in the box?’ “

He and UNMC colleagues published another article, “An Integrated Approach to Laboratory Testing for Patients with Ebola Virus Disease,” in the fall edition of Laboratory Medicine.

The clinical team was closely monitoring cardiopulmonary function and electrolyte balance – key to stabilizing Ebola patients. But, the NPHL was not a hospital lab. It wasn’t prepared to do those types of hourly clinical tests and, because of the infectious nature of Ebola those tests couldn’t be done in the hospital lab. Only tests that could be performed on instruments with closed-tube sampling capability were done in the hospital laboratory. No opening of tubes was allowed outside the BSL3 laboratory.

“Special risks had to be considered,” Dr. Iwen said. “We were primarily concerned about microdroplets generated by centrifuges and automated instruments, breakage of tubes and bottles during processing and laboratory accidents.

We performed a risk assessment on our instruments to determine if specimens became airborne during processing. A tiny amount of tainted blood can deliver an infectious dose to mucous membranes and the eyes.”

Another risk was the transportation of the specimens. The NPHL is located across campus, resulting in a one-hour delay of testing due to decontamination and transportation of the specimen.

Between the discharge of the first patient and the arrival of the second, a new BSL3 laboratory was set up in the biocontainment unit with an expanded menu of tests available.

“As always, advanced preparation establishes a firm foundation on which we could make changes as the situation evolved. An essential part of the training exercises was learning how to adjust to changing conditions,” Dr. Iwen said.

“The procedures that we developed resulted in a process adaptable to many clinical laboratories that may need to test specimens that could contain the Ebola virus.”
A UNMC research team has been working on one phase of a concerted U.S. effort to develop a vaccine for the Ebola virus, which has infected more than 21,000 people in West Africa and killed more than 8,600 people.

James Talmadge, Ph.D., an immunologist and professor in the department of pathology and microbiology at UNMC, conducted a 10-month research project through the University of Nebraska’s National Strategic Research Institute (NSRI).

Dr. Talmadge’s five-member research team worked on this project on behalf of the Chemical Biological Medical Systems-Joint Vaccine Acquisition Program (CBMS-JVAP) as part of NSRI’s mission of providing research support for countering weapons of mass destruction (CWMD).

The CBMS-JVAP is the U.S. Department of Defense (DOD) organization responsible for developing, producing and stockpiling Food and Drug Administration (FDA)-licensed vaccine systems to protect soldiers from biological agents. Ebola is a class A bioterrorism agent with a mortality rate that can be as high as 90 percent.

Development of a medical countermeasure against the Ebola virus strains – Zaire, Sudan and Marburg – has become a DOD priority.

Several vaccine platforms are being developed and tested in rodents and primates. CBMS-JVAP has focused on an approach based on the use of FDA-approved aluminum salt (alum) adjuvants together with a virus-like particle (VLP) platform technology developed at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID).

Dr. Talmadge said all vaccines that were studied by his team contained aluminum salt in them.

The UNMC team was tasked with optimizing, characterizing and providing an initial assessment of the identified vaccine formulation. This was successfully completed and provided significant insights into improved parameters for a filovirus vaccine and support for future developmental efforts.

“There are a number of different Ebola vaccines that are being developed,” Dr. Talmadge said. “Nobody can really say which ones will be functional in humans and primates. It’s too early to draw any final conclusions.

“We successfully completed our task and the information we gleaned now can be used by other research groups in the U.S. and hopefully will contribute to the ultimate development of an Ebola virus vaccine.”

The NSRI at the University of Nebraska is one of only 13 other University Affiliated Research Centers (UARC) established by Congress and administered by the Office of the Secretary of Defense.

Dr. Talmadge said the University of Nebraska has the only UARC in the country working on a vaccine for the Ebola virus.

“It speaks volumes that our university is involved in a project of world importance like this,” he said. “Ebola is a scary virus that is usually fatal within seven days after symptoms are expressed. With the potential for international transmission via air travel, it’s really important that we come up with a vaccine as soon as possible.”

The NSRI provides research and development services for the DOD and the U.S. Strategic Command in five core competencies that are critical to national security. Those core competencies are:

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

“The U.S. Strategic Command and the University of Nebraska created the NSRI for this type of research – to find solutions to serious chemical, biological, radiological and nuclear threats,” said NSRI Executive Director Lt. Gen. (Ret.) Bob Hinson. “NSRI will continue to work with the nation’s Combating Weapons of Mass Destruction-focused agencies to conduct cutting-edge research to deal with threats like the Ebola virus.”

For Steve Callicutt, USSTRATCOM Director for Capability and Resource Integration, the work being done is all about making the world a more secure place.
“The U.S. Strategic Command is charged with combating weapons that present the gravest danger to the American public, namely weapons of mass destruction,” he said. “From sensing the threat to eliminating the materials, we face a challenge that is multi-dimensional and complex.

“We recognize this is a long-term problem that will require focused research, analysis, experimentation and testing. To that end, we established the UARC to build the body of knowledge this nation will need to maintain security both at home and abroad.”

Faculty members from across the university, including UNMC, have attracted more than $9 million in contract funding to pursue 22 different projects. The UNMC-affiliated investigators include:

- **Steven Hinrichs, M.D.**, Stokes-Shackleford Professor of Pathology and Microbiology and department chairman, who coordinates the initiative’s core competency to detect chemical and biological weapons.
- **Ken Bayles, Ph.D.**, professor of pathology and microbiology, who studies next-generation anthrax vaccines.
- **James Talmadge, Ph.D.**, professor of pathology and microbiology, who works on strategies to better protect soldiers from biological weapons.
- **Marilynn Larson, Ph.D.**, assistant professor of pathology and microbiology, who develops screening assays for the diagnosis of tularemia, which, due to its highly infectious nature and widespread distribution, has the potential for use as a biological weapon.
- **Serguei Vinogradov, Ph.D.**, a research professor of pharmaceutical science, who researches better methods of detecting biological weapons so troops can more quickly protect themselves. In a related project, he explores the combination of commercial systems with systems still in the research phase to combat weapons of mass destruction.
- **Tony Sambol**, assistant professor of pathology and microbiology, who works to develop stronger processes to prevent, prepare for and respond to biological incidents that impact the Department of Defense.

**UNMC, Nebraska Medicine share Ebola expertise through online courses**

UNMC and its primary clinical partner, Nebraska Medicine, are sharing Ebola patient care and treatment best practices with hospital staff around the world through online education courses. The biocontainment unit team also will hold sessions — in collaboration with the Centers for Disease Control and Prevention’s (CDC) Clinician Outreach and Communication Activity (COCA) and Emory University — to train staff in more than 30 U.S. hospitals that have been designated as Ebola treatment centers.

COCA serves a wide range of clinical professionals, including physicians, nurses, physician assistants, pharmacists, paramedics, veterinarians, epidemiologists, public health practitioners, and state and local health department officials.

The medical center’s free online Ebola education courses are available through iTunes, as well as Moodle and the UNMC/Nebraska Medicine websites. The downloadable courses provide easy-to-understand instruction and resources for health care professionals and the general public.

“The protocols and procedures we have refined here at UNMC and Nebraska Medicine are helping to keep health care workers safe nationwide while dealing with potential and diagnosed Ebola cases,” said Jeffrey P. Gold, M.D., chancellor of UNMC and chairman of the Nebraska Medicine advisory board. “We want to share our expertise with the world.”

The two courses, The Nebraska Ebola Method for Clinicians and The Nebraska Ebola Method for General Public, provide instruction and information through videos and printable documents. New content is continually added as more information becomes relevant and available. Continuing education credit is available.

A series of webinars on best practices offered to Nebraska clinicians are archived at www.unmc.edu/ebola.

iTunes U is the world’s largest online catalog of free educational content from top schools and prominent organizations. Moodle.org is an open-source e-learning platform with about 65 million users worldwide.
Oh. So that’s what we’ve come to talk to him about. Chicken soup.

Dr. Rennard exhaled, and leaned back in his chair so his voice would carry into the open office door across the hall: “How do I feel about the chicken soup story, Lillian?”

After a knowing laugh, the answer: “It’s just been unbelievable,” Lillian said.

Dr. Rennard is Stephen Rennard, M.D., Larson Professor of pulmonary and critical care medicine at UNMC. Lillian is Lillian Richards, office associate I, internal medicine pulmonary, charged with wrangling Dr. Rennard, and sometimes (OK, often) also all this stuff about chicken soup.

And this chicken soup stuff never stops. It happened again, just the other day. This time it was Martha Stewart mentioning it in a syndicated “Ask Martha” column. Yes, Martha said. According to a “recent” University of Nebraska Medical Center study, chicken soup, while not a cure, could help alleviate symptoms of the common cold.

It never stops.

Go ahead, Google the words Rennard chicken soup and the search engine comes up with about 5,330 results in 21 seconds. None of them, as far as we can tell, are about any other Rennard or any other chicken or any other soup.

People love it that a scientist actually has studied whether chicken soup might be good for you when you have a cold, just like your mom says.

Dr. Rennard, UNMC’s inaugural scientist laureate, is a world-renowned chronic obstructive pulmonary disease (COPD) researcher. Well, he’s world renowned for his COPD research within scientific circles. To the rest of us, thanks to a 1993 study that’s proven to have gone not viral, but retroviral, he’s world renowned as Mr. Chicken Soup.

“That’s the funny part,” came Lillian’s voice, from across the hall.

It’s like a musician who has done great work for decades. But we, the public, can’t get that one, long-ago hit song out of our heads. Right?

Well, no, Dr. Rennard said. It’s not like that at all. “It would be kind of like,” he said, and then paused for a good 10 seconds, trying to think of what it would be like.

“Oh, so Charles Dodgson,” Dr. Rennard finally said. (Charles Dodgson? Pen name: Lewis Carroll.) “It’s kind of arrogant to compare yourself to somebody like that. But, he got to be really famous for ‘Alice in Wonderland.’”

“He was actually a serious mathematician,” Dr. Rennard said. “But nobody cares about that other stuff.”

This all happened because Dr. Rennard had also always heard the folk wisdom, from cultures all over the world, that...
Chicken soup has given Dr. Rennard three great career highlights, the kind few scientists are lucky to get:

- His wife Barbara, the study’s first author and head soup chef, always loved listening to Bob Edwards on National Public Radio (NPR). Guess who was interviewed by Edwards about chicken soup and managed to get his wife in on the call? “He talked to me for 10 minutes. He talked to her for the whole rest of the hour!” Dr. Rennard said. “And my wife’s friends were listening to NPR radio and said, ‘That’s Barbara Rennard!’ ”

- When Dr. Rennard’s hometown paper, the St. Louis Sun, was doing a chicken soup story for its Sunday magazine, it asked him for a photo. Well, it is his wife’s grandmother’s recipe, he said, and she was from St. Louis. How about a photo of her? It ended up being an old photo of Barbara Rennard’s grandmother cooking with her two young daughters, Barbara’s mother and aunt. Heartwarming stuff. “I got my mother-in-law’s picture in the newspaper, ” Dr. Rennard said. A man can’t do much better than that.

- Dr. Rennard and chicken soup are a question in Trivial Pursuit. Every parent can relate: of all the work he has done, it was nice to finally have something his kids thought was pretty cool. And so, Dr. Rennard will continue to work tirelessly on COPD ("It’s the third leading cause of death in the United States and it’s not a household word," he said). And he will continue to take phone calls about chicken soup.
An electron micrograph (25,000x magnification) of Ebola virus particles (green) attached to, and budding from, an infected cell (blue). Credit: National Institute of Allergy and Infectious Diseases.
Rare, but deadly, Ebola is a filovirus, one of four distinct families of hemorrhagic fever viruses. There are five different strains of Ebola. The most fatal virus is Ebola-Zaire, the virus that has caused more than 8,600 deaths this year, mostly in West Africa.

Outbreaks of Ebola have been occurring more and more frequently. The 2014 epidemic in West Africa is unprecedented in terms of its scale and the speed of its devastation. It has become an urgent global health problem.

While more than 4,000 proteins are in a typical cell or bacteria, the Ebola virus contains only seven distinct proteins of large molecules arranged in a long, braided, thread-like strand of negative RNA. One of these seven proteins is known as the nucleoprotein for its ability to interact with the viral RNA genome.

Scientists around the world have been studying the various strains of Ebola to gain a deeper understanding of the molecular biology of the virus, which could be critical in the development of vaccines or antiviral drugs to treat or prevent the disease.

James Talmadge, Ph.D., an immunologist and professor in the department of pathology and microbiology at UNMC, is one of these scientists (see story page 8).

He described how the Ebola virus works.

“Ebola is fragile and, like HIV, can only survive in a fatty (lipid) coating. But, Ebola does in 10 days what it takes AIDS 10 years to accomplish. From the time of infection to onset of symptoms is two to 21 days. You are not infectious until you develop symptoms. The first symptoms are like the flu – fever, fatigue, muscle pain, headache and sore throat. That’s when the virus is attacking the body’s immune system, destroying its ability to clot,” he said.

“Ebola is crafty. It stops the immune system from making antibodies and then starts copying itself like crazy. The virus grows uncontrollably and infects and destroys the organs and turns them into mush. That’s when the vomiting, diarrhea and rash appear. Eventually, every cell dies and explodes, releasing all their contents into the blood. This triggers a cytokine storm, the most extreme immune attack. That’s what kills you.

“At the end stage of the disease, you have internal and external bleeding, multi-organ failure and shock. Like it’s eating you from the inside out.

“Viruses are molecular sharks, a motive without a mind.”
James Wahl, Ph.D., is interested in how cells move.
Specifically, he is interested in epithelial cell adhesion – epithelial tissues include the skin as well as the inside of the mouth. “We’d like to know how these cells migrate in order to close cuts on the skin or in our mouths.”
In exploring how cells move, Dr. Wahl, an associate professor of oral biology and cell biologist at the UNMC College of Dentistry, may discover a way to limit metastasis of tumors of the mouth and tongue, as well as other tumors that originate in other epithelial tissues.
His project is funded by a three-year, $280,000 National Institutes of Health R15 grant.
“We’re interested in how cells stick together, how they adhere to one another,” Dr. Wahl said. “When tumor cells arise, they come apart from one another and gain the ability to metastasize. When epithelial cells are in a normal tissue, they stay put – so you maintain that epithelial lining.”
When cells are forced to migrate – when the skin is cut, for example – the cellular adhesive junctions are remodeled.
“We’re interested in how their adhesive strength changes during processes like wound healing, or how they’re altered during tumor cell metastasis.”
Early stage tumors that form an adherent mass are often easy to treat by surgical removal, Dr. Wahl said.
“The problem is when the tumor grows to the point where the cancer cells begin to migrate away from the primary tumor and start relocating to the rest of the body,” he said. “Then you get metastasis, which if we can limit, then hopefully we can slow things down and give chemotherapies more time to work.”
Dr. Wahl works with third-year dental student Elizabeth Sand and may draw more research help from University of Nebraska-Lincoln students (R15 grants are designed to bring students into the research process).
Healthy epithelial cells are tightly associated with one another, Dr. Wahl said. “Under a microscope, these junctions made of protein complexes or cell sheets, that hold the cells together and look static.
“But while we know a lot about the static snapshot of what these complexes look like, we don’t know how these adhesive junctions are remodeled – when cells have to detach from their neighbor and clamber into a wound, for example.
“We’re trying to figure out what are the control mechanisms that cause one cell to say, ‘Hey, I have to move over there.’ And then when it gets over there, how does it reestablish that junction to reform that cell sheet.
“So we’re looking closely at the signaling pathways that control adhesiveness.”
A center of excellence in research is not built overnight. Not even in five years or 10. It takes time.

That's why the National Institutes of Health (NIH) established the Centers for Biomedical Research Excellence (COBREs), to help universities build comprehensive research programs.

These centers are generally led by a principal investigator who is an established biomedical research scientist with expertise central to the research theme of the center. Key ingredients are collaborative and multidisciplinary projects, the funding and mentoring of young investigators, and the creation of an infrastructure that enhances core lab facilities at participating institutions.

COBRE grants are awarded in three five-year phases to assure that the Centers are fully developed at the end of the NIH support.

The COBRE program is part of the Institutional Development Award program which builds research capacities in states that historically have had low levels of NIH funding by supporting research development in undergraduate institutions and in graduate research institutions (COBRE).

The University of Nebraska currently has seven COBRE grants in various phases. These COBREs are centered at UNMC as well as at the University of Nebraska-Lincoln (UNL) and the University of Nebraska-Omaha. An eighth COBRE is based at Boys Town National Research Hospital (BTNPRH).

UNMC itself is home to one Phase II and two Phase III COBREs, one of which is a collaboration with investigators at BTNPRH and Creighton University. UNMC researchers also collaborate extensively on a fourth COBRE based at UNL (see story page 21), although many other collaborations have developed between faculty members associated with the COBREs.

**COBRE support comes in three sequential five-year phases:**

- **Phase I** focuses on developing research infrastructure and providing junior investigators with formal mentoring and research project funding to help them acquire preliminary data and successfully compete for independent research grant support.

- **Phase II** seeks to strengthen each center through further improvements in research infrastructure and continuing development and support of a critical mass of investigators with shared scientific interests. After 10 years of COBRE support, centers are expected to be able to compete successfully for other sources of research funding.

- **Phase III** transitional centers provide support for maintaining COBRE research cores developed during phases I and II, and sustain a collaborative, multidisciplinary research environment with pilot project programs and mentoring and training components.

Two of UNMC’s COBRE grants have reached phase III – the third has just entered phase II. Now that the last phase is reached, UNMC will apply this year for a new COBRE grant to build another area of excellence, said Jennifer Larsen, M.D., vice chancellor for research. The following stories recap the progress of UNMC’s three COBRE grants.
Shelley Smith, Ph.D., director of developmental neuroscience at UNMC’s Munroe-Meyer Institute and professor of pediatrics, recently learned her COBRE grant, “The Molecular Basis of Neurosensory Systems” was renewed for five years by the National Institutes of Health.

Now in phase III, the COBRE grant is smaller than Dr. Smith’s first two awards – $750,000 in direct costs.

“Phase III is sort of a winding down of the research support,” Dr. Smith said. “NIH figures by now you’ve got a core group of researchers who are on their way – they’ve been getting grants, they’ve been publishing, and they’re working together.”

Instead, there is more focus on the core facilities that support research for the scientific community such as facilities for DNA sequencing, histology and imaging, auditory physiology and mentoring.

There is limited research support in the form of pilot grants which are targeted toward helping researchers develop new projects.

“We’re also formalizing our mentoring program a lot more in phase III,” she said. In COBRE applications for phases I and II, the research projects are larger and are described as part of the grant, and the overall grant is judged partially on the quality of the researchers’ proposals.

“For phase III, you don’t propose the pilot grants,” Dr. Smith said. “You propose the structure for how you’re going to solicit them and judge them.”

Dr. Smith recently solicited applications for pilot programs. She expects to fund at least two, for a maximum of $100,000 each.

Since the overall scientific theme of the COBRE is neurosensory development, pilot programs should fit in this area.

“This includes areas such as the development and maintenance of the auditory system or visual system,” she said. “But also early development of the central nervous system, such as disorders related to autism and developmental disabilities.”

Selected projects will have to be approved by an internal steering committee, an external advisory committee and also the NIH.

The grant is funded by the National Institute for General Medical Sciences. Kirk Beisel, Ph.D., Creighton University, and Edward Walsh, Ph.D., Boys Town National Research Hospital, are co-investigators of the grant.
CELLULAR SIGNALING IS FOCUS OF COBRE

To Keith Johnson, Ph.D., director of the Nebraska Center for Cellular Signaling (NCCS) in the College of Dentistry, reaching phase III status, with a $4.9 million grant renewal, means the opportunity to turn a corner.

Jeffrey Payne, D.D.S., the College of Dentistry’s associate dean for research, said the phase III status and renewal of the National Institutes of Health (NIH) grant “will support collaborative research across UNMC colleges and departments in the area of cellular signaling and will facilitate the NCCS’ trajectory as a self-sustaining center.”

Through its first two phases, the COBRE also placed emphasis on development of promising young faculty – and Steven Caplan, Ph.D., Jixin Dong, Ph.D., and Aimin Peng, Ph.D., were among those who used NCCS support as a springboard to their first independent NIH R01-type funding.

In its phase III inception, the COBRE will now support projects with co-principal investigators of more or less equal expertise in different areas. The cross-multidisciplinary college collaboration is designed to help keep the momentum going, even after NIH funding eventually stops.

Additionally, the COBRE’s momentum was a factor in helping secure nearly $700,000 in funding from a Nebraska Research Initiative (NRI) grant in order for UNMC to acquire a new state-of-the-art super-resolution microscope. This microscope, which allows researchers to see things with up to 10 times greater resolution, offers tremendous opportunity for those who study cellular signaling. (See story page 20.)

“It is a potential game-changer for our COBRE,” said Dr. Johnson, who also works in the oral biology department. “What we look at is cell-cell adhesion events that happen at the cell surface.” And now NCCS investigators can see them like never before.

The program began in 2003, shepherded through Phases I and II by the late Margaret Wheelock, Ph.D. The three phases have totaled $25 million in grant money. The COBRE is currently funded through 2018, making the College of Dentistry a national leader in the study of cellular signaling in cancer.

in Pharmaceutics, UNMC College of Pharmacy, and co-director of the Center for Drug Delivery and Nanomedicine.

Nanomedicine uses a broad variety of well-defined nanostructured materials to deliver drugs, genes and diagnostic agents safely to the site of disease or injury.

“The continuing COBRE support will further solidify our efforts in the areas of drug delivery and nanomedicine,” said Dr. Bronich, who is the 2014 Scientist Laureate at UNMC.

“It allows us to continue our truly interdisciplinary research at the university.”

The grant will continue to help build a critical mass of investigators. Five junior investigators are supported through the grant along with two pilot projects that focus on prevention of surgical site infection and early detection of cancer.

In addition, the grant will support two research core facilities: the bioimaging core, directed by Michael Boska, Ph.D., radiology department; and the nanomaterials core, co-directed by Dr. Bronich and Dong Wang, Ph.D., pharmaceutical sciences.

Tatiana Bronich, Ph.D.
STORM CHASER

to headline
2015 Nebraska Science Festival

REED TIMMER IS AMONG THE FEW TO DOCUMENT BOTH AN F5 TORNADO AND THE MOST DEVASTATING HURRICANE IN U.S. HISTORY.

On April 10, he’ll share his experiences as a meteorologist and extreme storm chaser when he kicks off the third annual Nebraska Science Festival. This year’s festival runs April 10-18 and again features an array of science- and technology-related activities in communities across the state.

“This year’s festival will be bigger and better than ever,” said Kacie Baum, coordinator of the Nebraska Science Festival and science outreach programs coordinator at UNMC. “We’re planning lots of great educational activities and extending both the length and the geographic reach of the festival.”
Programming will be available for all ages and span hands-on activities, tours, talks and nature experiences (much of it free to the public). Already planned: the opportunity to walk through an 18-foot-long by 14-foot-wide by 12-foot-high inflatable brain at the April 18 Science Expo, attend a science of beer talk (adults only) or engage preschoolers in a Little Scientist Expo.

For those who love science, why wait until April? Teenagers can create a 30-second video explaining what a germ is to a fifth-grade audience. Scientists can volunteer to share their expertise with middle schoolers. And, fourth- through 12th-graders can enter the SciFest essay contest for a chance to meet Timmer, who has appeared on the Discovery Channel’s Storm Chasers and When Nature Strikes.

Today, Timmer is CEO of Weather Fusion, LLC and Extreme Tornado Tours, LLC, offering forensic meteorology and consulting services, extreme weather media, and storm chasing tours. His tornado, hurricane, and blizzard footage has been licensed to more than 100 production companies and television networks since 1997, and has been seen by hundreds of millions of people worldwide on television, Internet and mobile video devices. He also is working on a Ph.D. in meteorology from the University of Oklahoma.

Presented by UNMC, the Nebraska Science Festival is a collaboration of organizations and individuals interested in the advancement of science literacy. The Science Festival is designed to make science accessible, interactive, relevant and fun for kids and adults alike.

In addition to UNMC, other sponsors, to date, include Nebraska Medicine, the Nebraska Coalition for Lifesaving Cures, Metro Credit Union, HDR, West Corporation and media sponsors KETV and the Omaha World-Herald.

In addition to the web site, updates also are available on Twitter (@NESciFest) and Facebook (NE SciFest).
Super microscope yields higher level of detail

UNMC has acquired a state-of-the-art microscope which increases resolution by three to 10 times what was previously available on campus.

Keith Johnson, Ph.D., professor of oral biology and director of the Nebraska Center for Cellular Signaling in the College of Dentistry, said the new instrument allows UNMC to go toe-to-toe with academic health science centers across the world.

“We’re competing with the best,” Dr. Johnson said. “This will put us in the game.”

Nearly $700,000 in funding from a Nebraska Research Initiative grant, plus additional monies from the NCCS, paid for a Zeiss ELYRA PS.1 super-resolution system, housed in the UNMC Advanced Microscopy Core Facility (encompassing both confocal and super-resolution imaging technology). Having it on campus gives UNMC a leg up in competition for research funding and in recruiting sought-after researchers to campus.

This microscope’s capabilities will be the gold standard in five years or so — putting UNMC ahead of the curve in a field that continues to advance.

“We’re going to be able to distinguish between structures inside the cell that previously might have looked as though they were overlapping or in the same place,” said Steve Caplan, Ph.D., director of the Core Facility and professor of biochemistry and molecular biology. “Now we’re going to be looking at a higher level of detail. This is crucially important for the fundamental understanding of how cells work.”

Drs. Florescu, MacTaggart win top honors at Innovation Awards

Marius Florescu, M.D., took home the 2014 Emerging Inventor Award, while Jason MacTaggart, M.D., received the Most Promising New Invention Award during UNeMed’s eighth annual Innovation Awards Ceremony in October.

Dr. Florescu, associate professor of nephrology, received the Emerging Inventor Award for two of his recent inventions: A hemodialysis catheter and a device to improve the arteriovenous or AV fistula.

The new hemodialysis catheter tube is designed with a small balloon that can expand to remove the build-up that naturally grows into a mass that blocks flow. Dr. Florescu’s innovative design would significantly lower the cost of removing the blockage by eliminating the need for additional procedures.

The new design for the AV fistula is the first major improvement in 40 years in the area. AV fistulas are made by surgically creating a portal between a vein and artery, usually in the wrist, for patients who must undergo regular hemodialysis.

Dr. MacTaggart, assistant professor of vascular surgery, was awarded the Most Promising New Invention Award for his new surgical tool, the AquaBlade. The tool is designed to cut tissue amid flowing blood using highly-pressurized water. The device also can be used to remove stents in blood vessels. The AquaBlade is less invasive, which lowers risk factors associated with heart surgery and speeds the patient’s recovery process.
Researcher heads $3.3 million national study in rare pediatric diseases

UNMC researcher William Rizzo, M.D., has received a five-year, $3.3 million grant to study 10 rare diseases that affect children beginning in infancy or early childhood and throughout their life.

Dr. Rizzo is part of a consortia of 22 researchers who will collaborate with 98 patient advocacy groups to advance clinical research and investigate new treatments for children with rare diseases. The collaborations are made possible through $29 million in grants from the National Institutes of Health to expand the Rare Diseases Clinical Research Network, which is led by NIH’s National Center for Advancing Translational Sciences (NCATS).

The diseases Dr. Rizzo treats and studies are probably unfamiliar to most people. They influence the pathway for cholesterol synthesis and metabolism and include diseases such as Sjogren-Larsson syndrome, Smith-Lemli-Opitz syndrome and Hyperimmunoglobulinemia D or Hyper-IgD syndrome. Some of the diseases cause intellectual disabilities, behavior changes and/or physical problems. One disease causes recurrent fevers and rash every four to six weeks for a lifetime.

He said some of the diseases each affect between 500 to 1,000 children nationwide, while others affect fewer.

UNMC, UNL collaborate on obesity COBRE grant

The University of Nebraska-Lincoln has earned an $11.3 million grant from the National Institutes of Health to establish a research center focused on understanding nutrition and obesity at the molecular level, and UNMC researchers will collaborate on the project.

The five-year grant from NIH’s Center of Biomedical Research Excellence (COBRE) program will support the Nebraska Center for the Prevention of Obesity Diseases through Dietary Molecules (NPOD). The COBRE program is funded through the Institutional Development Award Program, which supports health-related research and fosters faculty development and research infrastructure.

Justin Mott, M.D., Ph.D., assistant professor of biochemistry and molecular biology at UNMC, serves as a project leader in the NPOD. Dr. Mott studies liver injury associated with obesity and metabolic syndrome, which also is called non-alcoholic fatty liver disease (NAFLD). Non-alcoholic fatty liver disease is the most common cause of liver injury and can result in liver failure and even liver cancer.

“A new therapy requires knowing the natural progression of the disease. We will learn what happens over time to patients — medical problems and complications and what therapies will be required,” he said. “In many diseases, there’s no specific therapy that works. A physician may see only one or two patients with this disease in the course of his or her career.”

According to the NIH, there are several thousand rare diseases, of which only a few hundred have any treatments available. Combined, rare diseases affect an estimated 25 million Americans.
Neck manipulation may be associated with strokes

Treatments involving neck manipulation may be associated with stroke, though it cannot be said with certainty that neck manipulation causes strokes, according to a scientific statement published in the American Heart Association’s journal Stroke.

Pierre Fayad, M.D., professor in the UNMC Department of Neurological Sciences and director of Nebraska Medicine’s Stroke Center, was part of the 13-member team that co-authored the statement.

The group was headed by Jose Biller, M.D., of the Loyola University Health System in Chicago, and Ralph Sacco, M.D., of the University of Miami Hospital, with other members representing the Mayo Clinic, Washington University in St. Louis, the University of Connecticut, Tufts University, and the University of Kansas, among others.

Cervical artery dissection (CD) is a small tear in the layers of artery walls in the neck. It can result in ischemic stroke if a blood clot forms after a trivial or major trauma in the neck and later causes blockage of a blood vessel in the brain.

“Cervical artery dissection is an important cause of stroke in young and middle-aged adults, and it is often unrecognized,” Dr. Fayad said.

“Most dissections involve some trauma, stretch or mechanical stress,” Dr. Biller said. “Sudden movements that can hyperextend or rotate the neck – such as whiplash, certain sports movements, or even violent coughing or vomiting – can result in CD, even if they are deemed inconsequential by the patient.”

Although techniques for cervical manipulative therapy vary, some maneuvers used as therapy by health practitioners also extend and rotate the neck and sometimes involve a forceful thrust.

There are four arteries that supply blood to the brain: the two carotid arteries on each side of the neck, and the two vertebral arteries on the back of the neck. The influence of neck manipulation seems more important in vertebral artery dissection than in internal carotid artery dissection.

“Although a cause-and-effect relationship between these therapies and CD has not been established and the risk is probably low, CD can result in serious neurological injury,” Dr. Biller said. “Patients should be informed of this association before undergoing neck manipulation.”

The American Association of Neurological Surgeons and the Congress of Neurological Surgeons endorse the scientific statement.

UNMC team’s vancomycin study highlighted in JAMA

UNMC research team has determined that a longtime antibiotic, vancomycin, is still effective in treating Staphylococcus aureus bloodstream infections and that physicians should continue to use the drug even though several newer antibiotics are now available.

The research was reported in the Oct. 15 issue of The Journal of the American Medical Association, one of the leading research journals in the country.

Andre Kalil, M.D., professor in the UNMC Department of Internal Medicine and an infectious diseases specialist, led the four-person UNMC team. Two other infectious diseases specialists – Mark Rupp, M.D., professor, and Trevor VanSchooneveld, M.D., assistant professor – and Paul Fey, Ph.D., professor, pathology and microbiology, assisted him.

Staphylococcus aureus is among the most common causes of health care-associated infection throughout the world. It causes a wide range of infections, with bloodstream infections among the most common and lethal.

For more than 50 years, the primary therapy for Staphylococcus aureus infections has been either semisynthetic penicillins or vancomycin.

“The study provides strong evidence that vancomycin remains highly useful,” Dr. Kalil said. “Even though vancomycin is an older drug, it is still killing staph very efficiently. There are newer antibiotics available to treat Staphylococcus aureus infections, but this study demonstrates that physicians don’t necessarily need to switch to these new drugs when the minimum inhibiting concentration is increased but still within the susceptible range.

“The prevention of a rapid switch to newer drugs has another great benefit to our patients – less unnecessary exposure to these drugs, which will translate into less development of antibiotic resistance.”
I asked him to take me to Kikwit, Zaire, back in the year 1995, to the second outbreak of Ebola-Zaire. To viral ground zero.

He closed his eyes and took a deep breath. He began to speak, slowly at first, and then his pace increased as images sharpened in his mind.

“Kikwit was the regional capital, but the country had collapsed after years of economic and political crisis. The city of dirt streets and wood huts with rusted metal roofs had reverted to small farms growing cassava, a starchy vegetable. Many old significant buildings were empty,” he said.

Ali S. Khan, M.D., M.P.H., dean of UNMC’s College of Public Health, was, at the time, a rising star in the Centers for Disease Control and Prevention. He was 31 and already the epidemiology chief of the Special Pathogens Branch.

He had just returned from South America, where he worked with the hantavirus, a severe, sometimes fatal respiratory disease in humans transmitted by rodents. Suddenly, the disease detective was part of a four-man team assigned to control an even deadlier outbreak halfway around the world.

It was the same virus subtype that had broken out in 1976 in the northern part of the country, along the Ebola River, which gave the virus its name.

“I was honored to be given the opportunity to go in the first group. We wanted to understand why the virus reappeared after 20 years, challenge how it was transmitted and learn how to contain it.”

Enroute to, and in, Kikwit, the four medics quickly discovered that Ebola had captured the imagination of the press. Media teams outnumbered public health people at least seven to one. “It was embarrassing,” Dr. Khan said. Over the next two months the health care team grew to 30.

His first time in Africa, Dr. Khan’s job was to identify patient zero and attempt to determine the natural reservoir – from which the disease had come. He had one major drawback – he couldn’t speak French and would need an interpreter. Fortunately, two other teammates knew the language.

The hospital consisted of 10 separate pavilions with corrugated tin roofs connected by covered walkways.

“It was deserted. We found only one health care worker who was treating patients. The others had fled. People were lying on mattresses, no sheets, on metal beds. The living were among the dead. Vomit, diarrhea and blood covered the floors and walls. It was horrible.”

Dr. Khan worked 12- to 14-hour days tracking down who infected whom. He eventually identified patient zero, a farmer and brick maker who probably had been infected by a bat and passed it on to at least 20 family members and hospital workers.

“We identified every mechanism of transmission (body fluids) and set up procedures to stop the spread,” Dr. Khan said.

Ebola occurs all the time in Africa, but it usually doesn’t infect more than one or two humans. The trouble is when it gets into the health care setting it becomes, what Dr. Khan was first to describe, a “super spreader” – infecting five or more people.

The virus was spread easily at the hospital with the constant reuse of needles to administer medicine for the ever present malaria.

“This was my first major outbreak of a virulent disease, and it was transformational. It defined the rest of my public health career – going from village to village, seeing people dying from malaria, and no one cares because it’s not Ebola.”

Malaria, an entirely preventable and treatable illness, caused an estimated 627,000 deaths in 2012, mostly in sub-Saharan Africa. Closer to home, West Nile Virus, a fatal neurological disease in humans, is monitored annually in Nebraska, where 226 people were infected and five died of the disease last year.

Both are spread by mosquitos, the super spreader of the world. Two large wire sculptures of the insects decorate Dr. Khan’s office wall as a constant reminder of the danger in our own back yard.
At the University of Nebraska Medical Center, our faculty may indeed wear white lab coats, but they are by no means sequestered from the real world. Whether on the forefront of cancer research, helping mitigate an international health crisis or working to solve the shortage of health care professionals in rural areas, they are in the thick of the fight – bringing experience, technology, compassion and innovation wherever they are needed most. Given our geographic location, some might call it leading from the middle. We just call it good health care. **UNMC. Breakthroughs for life.**