

Advancing the science of medicine

Quality, innovative research will set Avera apart as a leading hospital

BY DONNA FARRIS, AVERA MCKENNAN WRITER/EDITOR

Leading hospitals are known for cutting-edge medical research – just as they are known for excellence in heart, stroke or cancer care. Every day, medical researchers make discoveries that continually advance the science of health care.

It's happening at institutions such as Cleveland Clinic and Mayo Clinic... and it's happening in Sioux Falls at the Avera Research Institute.

"A hospital's reputation is built to a great extent on the research they are conducting. It's an integral part of a large health system," said David Kuper, executive director of the Avera Research Institute.

And so the Avera Research Institute is not interested in simply having a few token research projects to be able to say that research is going on here.

Rather, the institute is building a research "pipeline," which flows from basic research – where ideas are born, to applied research – where useful applications are identified and developed, to clinical research – where products are tested and approved, said Dr. Kaia Kloster, director of the Applied Research Division.

Cutting-edge technology, rather than the status quo, is what sets

leading research institutions apart, Kloster said. "I think it's very insightful, very visionary of Avera to be interested in pursuing this type of endeavor."

Kuper put together a business plan, and when the Avera Research Institute started in October 1998, it was comprised of himself and a part-time nurse. "Now we have three divisions, eight PhDs and 50-plus employees."

The foundation of almost all clinical knowledge is basic research into the function of cells and organs. Three areas of focus in the institute's Basic Research Division include obesity-related kidney disease; neuroscience research in the area of stress-related sleep disorders and cocaine addiction and oncology research involving DNA repair for skin cancer. Such work is funded through grants by the National Institutes of Health and other sources.

Innovative ideas to new products

The Applied Research is more entrepreneurial in nature, with a goal of developing products for commercialization.

Kloster heads this division, now working to develop a medical adhesive which can either bind tissue to tissue,



Cutting-edge treatments offer new hope for cancer patients

Until there's a cure for cancer, each new drug and each new treatment represent new hope for patients who battle this potentially fatal enemy.

Clinical research in the area of oncology has been a major area of growth in the Avera Research Institute.

In 2003, there was one study open. Today, in 2007, there are approximately 30 ongoing trials.

"The criteria for each study are different and very specific," said Jessica Larsen-Gallup, oncology research coordinator. Because of the specific criteria, some studies at Avera involve very few subjects, and their results are pooled with other sites from across the United States and the world.

Dr. Vinod Parameswaran, Avera McKennan hematologist, said drug trials help him deliver optimum care to patients, and he's seen it make a difference in his patients' outcomes. Patients who participate not only gain access to promising new treatments, they help medical science to make significant advances in the fight against cancer.

What: Avera Research Institute

Who: Eight PhDs and 50 employees working in three divisions, having grown from one founding director and a part-time nurse in 1998.

Why: At the Avera Research Institute, innovative ideas are born, useful applications are developed and applications are tested for four key reasons:

- To distinguish Avera McKennan as a leading hospital.
- To offer the latest, up and coming, cutting-edge treatments.
- To make a lasting contribution to the science of medicine in fields such as cancer, infectious disease, kidney disease and psychiatry.
- To ultimately improve our health and quality of life.

"A HOSPITAL'S REPUTATION IS BUILT TO A GREAT EXTENT ON THE RESEARCH THEY ARE CONDUCTING. IT'S AN INTEGRAL PART OF A LARGE HEALTH SYSTEM." – DAVID KUPER

or tether drugs to tissue. Researchers are putting the focus on applications in ophthalmology, but the adhesive likely could have additional medical uses, Kloster said.

A growing reputation

The largest division is Clinical Research. “At any give time we have 30 to 40 clinical trials being conducted in a wide variety of therapeutic areas, from dermatology, to oncology, to infectious disease to rheumatology to pulmonology to behavioral health to nephrology,” Kuper said. Growing clinical research starts with good research design and ends with quality data. “Then it becomes word of mouth. You build upon your reputation.”



A major focus within Clinical Research is industry-sponsored clinical drug trials, which are either in Phase 2, 3 or 4 of the Food and Drug Administration approval process.

Phase 2 and 3 studies, which test dosage, efficacy and safety, are conducted by pharmaceutical companies prior to getting drugs FDA approved. Phase 4 studies follow FDA approval, perhaps looking at new indications for a drug or new dosage forms.

Growth naturally happens as the Avera name is solidified with pharmaceutical companies and government agencies. “They want to see quality and experience,” said Ryan Hansen, director of the Clinical Research Division. “We’ve established ourselves with our high-quality research, and we have physicians within any specialty who have experience conducting clinical research.”

Patients participating in research receive the same high quality of care given to all Avera patients. “We make sure any research that is conducted is done in a high quality manner, and that we’re providing the best possible care and protecting subjects in the best possible way,” Kuper said.

Up-and-coming treatments

Patients are attracted to research opportunities because they receive cutting-edge treatments not otherwise available to them, Hansen said. “We are often testing the new up-and-coming treatment for a specific disease or disorder.”

Physicians are motivated to further the advancement of medical science while giving their patients access to new and otherwise unavailable treatments. Patients often say that if they themselves can’t be helped by the treatment, someone in the future could be – perhaps their own grandchildren.

Military personnel and veterans may someday benefit from federally-funded research on Gulf War illness. The Avera

Cutting-edge treatments offer new hope for cancer patients (cont.)

Examples of cutting-edge cancer studies at Avera:

- The Avera Research Institute placed the first patient in the world on a graft versus host disease study for post bone marrow transplant patients. This study is looking into the use of photopheresis – exposure of a chemical to light, which is then mixed with blood to go back into the patient’s body. While the precise mechanics are still being studied, it appears that the treated white blood cells may actually bring the immune system into balance by reducing the activity of overactive immune cells.
- After taking part in a study of electroporation, a patient with cancer of the larynx went into remission. In this approach, the tumor is injected with a drug, and then basically electrocuted to open the pores within the tumor cells. This allows local saturation of the drug, rather than giving a powerful drug systemically. A concentrated dose of the drug goes directly to the tumor, and much less goes to the patient’s body.
- The institute recently opened a new trial for relapse refractory multiple myeloma, using an organic arsenic drug. “It’s something the physicians are excited about, especially for patients who have gone through every treatment option available, when the older chemotherapies in different combinations have failed,” Larsen-Gallup said.

Dr. Parameswaran hopes to expand Avera clinical research in the area of investigator-initiated studies. He has written a study protocol, with approval from the National Bone Marrow Transplant Registry, for a Phase 1 study, using an FDA-approved drug which is standard treatment for myelodysplastic syndrome, after a bone marrow transplant for leukemia patients.

Safety is an overriding concern with all drug studies.

After a lengthy consent process, patients know what to expect, and any cautions involved. Studies are very closely controlled, with patients carefully monitored.

Hope is often the motivator that interests patients in cancer drug trials – hope that it will work to fight their own illness, or to help someone in the future, Larsen-Gallup said. “Many patients do it to help themselves, but also for future generations,” she said.

Research Institute's part involves a clinical trial with fibromyalgia patients, who have similar symptoms of Gulf War illness, like chronic pain, fatigue and insomnia. The study will evaluate the health and economic benefits of adding cognitive and behavior therapy delivered either by an Internet website or by telemedicine to the standard medical care for fibromyalgia.

In the future, it's hoped to develop home-grown studies at the Avera Research Institute, in which local physicians take the lead.

"Our goal would be to do more investigator-initiated studies, working with our medical staff, writing our own protocols and facilitating our own hypotheses," Hansen said.

Why research?

The importance of medical research becomes very personal in considering where we or our loved ones would be without it.

"When my son, who has cystic fibrosis, was diagnosed at age 9, the average longevity for people with that disease was 18 years of age," Kuper said. "He is now 37, and he wouldn't be alive today if it weren't for the new antibiotic classes that have come out over the last 20 years."

"Medical research improves quality of life, improves longevity, reduces mortality of disease, and improves medical care," Kuper said. "If we didn't have research, medicine would not be where it is today."



Research continues to unlock mysteries of the mind



Psychiatry, the top service line at Avera McKennan, will soon become a top focus of research as well.

The foundation is being laid for Avera to become a Center of Excellence for psychiatric research in two initiatives – the development of the Avera Psychiatric Research Center as part of the Avera Research Institute, and the new Avera Institute for Human Behavioral Genetics (Avera IHBG).

Research is natural outgrowth of Avera's already exceptional offerings for behavioral health care, including the state-of-the-art Avera Behavioral Health Center and a number of psychiatrists and psychiatric specialists.

"Our behavioral health network of care is one-of-a-kind in the nation," said Ryan Hansen, director of Clinical Research at the Avera Research Institute.

Currently, the Avera Psychiatric Research Center is conducting two studies involving Alzheimer's disease, and two on schizophrenia. In the future, studies will address depression, anxiety disorder, obsessive-compulsive disorder and bipolar disease.

"We provide exceptional behavioral health care to our community and the surrounding region. We believe a very important part of that is providing research and adding to the scientific knowledge of behavioral health," Hansen said.

Pharmaceutical trials will lead to better care for various psychiatric disorders, and more treatment options for patients.

The development of the Avera IHBG coincides with building a research infrastructure in behavioral health. The emphasis of that center is to combine genetic research with clinical intervention to provide a better community and higher quality of life, Hansen said.

As the first genetics research institute in the state of South Dakota, the Avera IHBG is unique in that it combines the study of genetics and environment in a program that is family and community based, with treatment strategies that bridge the gap between genetic research and medical action.

The overall mission of the center is, through the use of careful behavioral, environmental and genetic assessment of children, families and communities, to reduce the burden of emotional and behavioral illness in the community.

This type of cutting-edge research has come about only in recent years since the mapping of the human genome, completed in 2000. While the use of genetic profiles has long been used in the field of physical medicine, this work is still in its infancy in psychiatry.

The Avera IHBG will use advanced genetic and psychiatric study to develop solutions to help prevent and treat disorders such as schizophrenia, bipolar disorder, ADHD, depression, addiction and anxiety. Dr. James Hudziak, internationally-known psychiatrist and genetic researcher, is scientific consultant for the new institute. He describes the Avera IHBG's work as a low-risk, high-yield program that is family based, focusing on educational and wellness programs.

Psychiatric illness is nearly always influenced by genetics as well as environment. Once the genetic component is understood, environmental factors can be addressed to help prevent illness.

"Our goal is to keep the well well, protect those at risk and intervene on behalf of those who are ill," Hudziak said.

Algae studies could lead to skin cancer breakthroughs

Skin cancer – the most common malignancy in the United States – will strike one in five people during their lifetime. This year alone, 1.3 million new cases will be diagnosed. Basic research at the Avera Research Institute is looking into reasons why sun damage results in skin cancer for some people, but not in others.

Human skin cells were designed with built-in repair processes to fix sun damage. When that damage goes unchecked, however, mutations occur, potentially resulting in skin cancer.

Dr. Jason Petersen, Avera Research Institute research scientist, is studying ultraviolet damage in unicellular alga, called *Chlamydomonas*, to better understand how UV light affects human skin cells.

“The UV component of sunlight has energy that can cause DNA damage and DNA damage can lead to mutation which can eventually lead to cancer.”

However, there are mechanisms within this alga and also within the human body to repair DNA damage caused by UV light.

“So we’re trying to better understand the repair process in *Chlamydomonas*, which can eventually apply to humans in trying to understand exactly why in certain instances the damage is not recognized and that it can lead to cancer.

The goal is possible medication someday to make DNA repair mechanisms more efficient and reduce the incidence of skin cancer.

Basic research begins with trying to understand how the cells and organs of the body function.

“As you begin to understand that, it eventually can lead to treatments.”

Petersen is among researchers around the world working on DNA repair, and his work will someday add to the body of knowledge on this subject.

His work at Avera is a continuation of his graduate school work, when he was involved in discovering a new gene in *Chlamydomonas* involved in DNA repair that had never before been characterized. After publishing that work, other researchers have found that when that particular gene is mutated in humans, it leads to a disease called trichothiodystrophy, characterized by brittle hair, mental retardation and developmental growth retardation.

“That’s why we do what we do. Unfortunately, a lot of people don’t understand and say, ‘Who cares – it’s algae.’ But with the idea that what we learn in algae can be applied to humans as well, our long-term goal is helping the health of humans.”

While Petersen is working toward answering a specific hypothesis which can be published to add to the body of knowledge, research involving DNA damage and skin cancer could go on indefinitely.

“Research is truly like an onion. You discover one thing, and that leads to five more questions. It’s a puzzle that continues to unravel.”



New biomaterial could change the practice of ophthalmology

By developing marketable medical products that will one day hit pharmacy shelves and hospital supply closets, Avera will join the ranks of those institutions that change the way health care is done.

“It’s truly state-of-the-art technology happening right here at the Avera Research Institute, right here in South Dakota,” said Dr. Kaia Kloster, director of the institute’s Applied Research Division, which is currently developing a biomaterial to be used as a tissue adhesive or a drug delivery mechanism for the eye.

“It’s a blend of chemistry expertise to build unique biomaterials, and physiology expertise to test it in biological systems,” Kloster said.

The technology has the potential to minimize or eliminate the need for sutures, advancing new ways to effectively and quickly close wounds – reducing pain and promoting healing.

While the adhesive has several possible applications, including cardiology, dermatology or urology, researchers are currently focusing on ophthalmology.

The adhesive could be used to close tissue after a cataract surgery, or to adhere medications to the eye.

“Your eye normally tries very hard to keep foreign materials from entering into the eye,” Kloster said. Because of the natural blinking and tearing response, only a small percentage of the drug in an eye drop actually makes it into the eye.

In tests, the adhesive can keep medications on the eye for at least an hour and in some cases, up to 16 hours. This would greatly enhance the effectiveness of eye medications.

“The industry has been looking for an adhesive for the eye for 40 years. To have something that is effective enough and safe enough has been the challenge,” Kloster said. Products to date are either strong enough, but not safe, or safe but not strong enough.

“That’s where we’re really hoping to make a difference in that industry. We could probably list a dozen different uses that would change how ophthalmologists currently practice,” she said.

The project was selected as one of Gov. Mike Rounds’ 2010 Initiative Research Centers of Excellence, in cooperation with South Dakota State University, the University of South Dakota and PhotoBioMed, based in Dallas, Texas. Since receiving funding through that initiative three years ago, the Applied Research Division has set aside other possible applications of the biomaterial for later study, although there are very promising applications for vascular surgery or balloon angioplasty, for example.

The biomaterial is “platform” technology in that diverse applications could come from it.

“Our motto has been focus and finish,” Kloster said. “Right now we’re emphasizing one unique and very promising product line to pave the way for whatever else might come down the pike.”



“IT’S TRULY STATE-OF-THE-ART TECHNOLOGY HAPPENING RIGHT HERE AT THE AVERA RESEARCH INSTITUTE, RIGHT HERE IN SOUTH DAKOTA.” – DR. KAIA KLOSTER