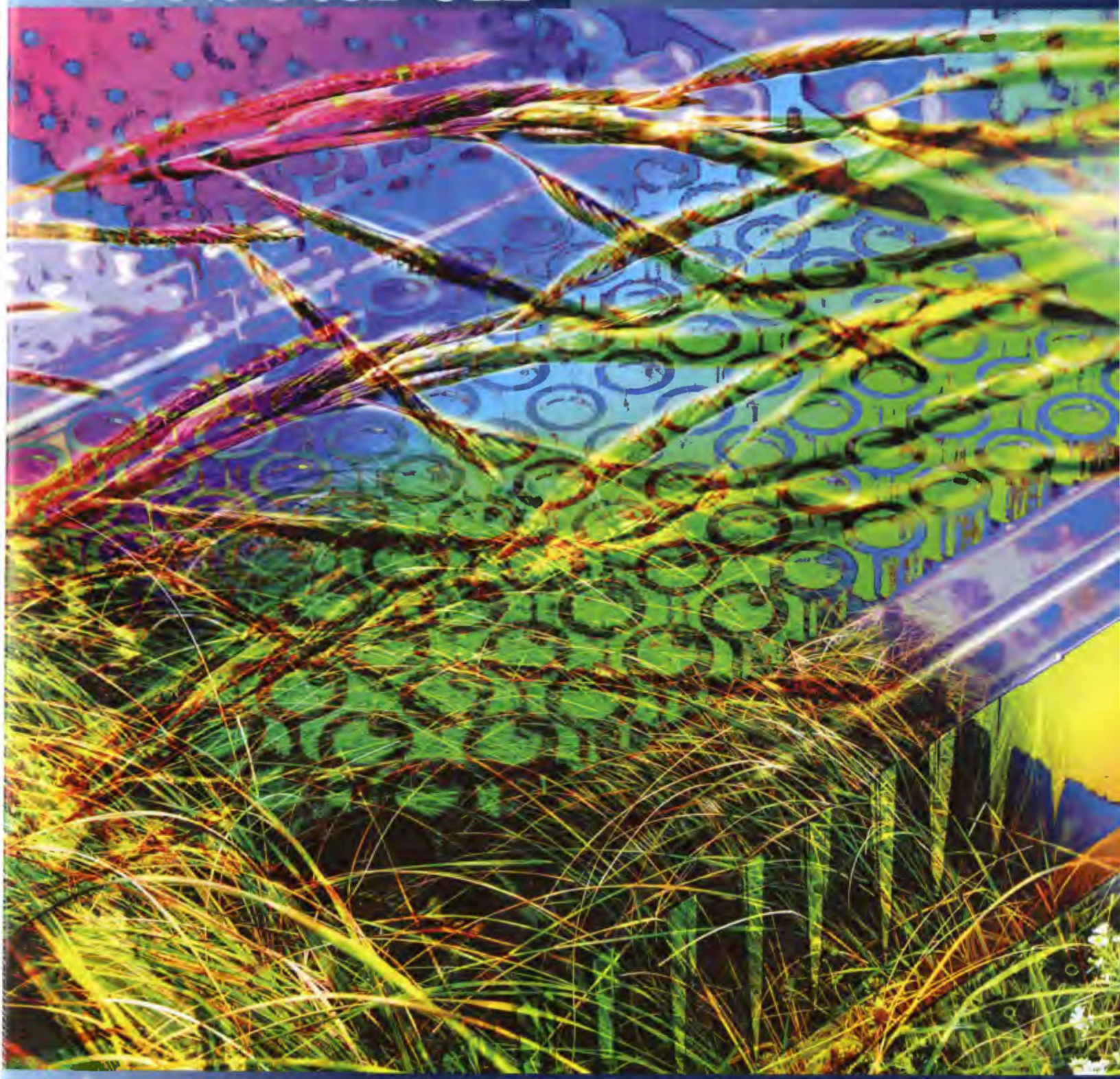
Research

SOUTH DAKOTA STATE UNIVERSITY



South Dakota State University
Spring 2017

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SOUTH DAKOTA STATE UNIVERSITY
SDSU
SPRING 2017

Pharmacy researcher investigates how

ASPIRIN KILLS CANCER CELLS

Jayarama Gunaje

Patients taking a low-dose aspirin daily to protect against strokes and heart attack get an added bonus—a reduction in their risk of developing cancer, particularly colorectal cancer.

This association has fueled research to determine the molecular pathways through which aspirin prevents cancer development, according to associate pharmaceutical sciences professor Jayarama Gunaje. "This observation has attracted the attention of physicians, scientists and the public alike—everybody is interested."

More than 1.6 million Americans are diagnosed with cancer and nearly 600,000 of those patients die every year, according to the American Cancer Society.

"We know how aspirin decreases inflammation and heart attacks, but no one knows clearly how it prevents cancer," Gunaje said. He began unraveling the molecular mechanisms through which aspirin prevents cancer in 2006 when he was at Texas Tech University. He came to SDSU in 2011.

While at Texas Tech, Gunaje's research was funded by National Institutes of Health grants. His research at South Dakota State has been supported by the Translational Cancer Research Center and the Scholarly Faculty Excellence Fund. Two doctoral students, Guoqiang Ai and Rakesh Dachineni, have worked on these projects.

Only two drugs—tamoxifen and raloxifene—have been developed to prevent cancer recurrence, with both targeting breast cancer. What Gunaje and other scientists discover may help identify and develop new cancer-preventing drugs/compounds.

Moving toward cancer

In the 1980s, an Australian study reported that people taking aspirin daily were 40 percent less likely to develop colorectal cancer than those who did not adhere to this regimen, Gunaje recalled.

More recently, a 2010 study in the United Kingdom analyzed data from 51 trials in which patients took a low-dose aspirin daily for five years and found 37 percent fewer deaths from cancer. However, Gunaje noted, these studies were not designed to directly assess the molecular mechanisms through which aspirin prevents cancer.

Evidence about aspirin's impact on colorectal cancer, in particular, led to the U. S. Preventive Service Task Force recommending the use of low-dose aspirin as a means of preventing cardiovascular disease—and colorectal cancer—for some adults, ranging from 50 to 69 years old. This is the first time that a major American medical organization has suggested aspirin as a means of preventing colorectal cancer in average-risk adults, according to a February 2016 New Hampshire Comprehensive Cancer Collaboration article.

Blocking enzyme, proteins

Essentially, aspirin inactivates enzymes known as cyclooxygenases, or COX, through a process known as acetylation. That then decreases the synthesis of prostaglandins, which are responsible for pain, inflammation and fever, Gunaje explained. This mechanism also prevents the formation of blood clots by permanently inactivating platelets.

Given this information, Gunaje and his team explored whether aspirin inhibits the functions of other proteins. For instance, protein p53 acts as a tumor suppressor. An estimated 50 percent of all cancers have mutated p53, meaning the protein is inactivated. "That favors cancer cell growth," he pointed out.

Using colorectal cancer cells, Gunaje and his team found that "aspirin acetylates p53 and reactivates the mutant p53, thus restoring its function as a tumor suppressor. This is a significant finding because lots of companies are interested in reactivating p53 as a strategy to treat cancer."

Exploring binding, inhibiting powers

Aspirin is made of two components, acetyl and salicylic acid groups. "Salicylic acid is a hormone in plants that helps prevent infection," Gunaje said, noting that it was originally extracted from willow tree bark. It is also present in apples, kiwi, cranberries, strawberries and other berries.

Aspirin is absorbed intact in the gastrointestinal tract and later broken down into acetate and salicylate ions in the liver and blood plasma, he said. "We think aspirin's ability to decrease cancer can be attributed to the intact aspirin and salicylic acid or its metabolites, which are formed in the liver."

To investigate salicylic acid's possible cancer-fighting targets, Gunaje looked at two proteins that work together to regulate cell division—cyclin-dependent protein kinase 2, or CDK2, which binds to cyclin A2 in body cells. This interaction increases the activity of CDK2, thus signaling the cell to proceed to the next stage of cell division.

Other researchers found that both CDK2 and cyclin A2 are either deregulated or upregulated in breast, liver and lung cancers. Therefore, inhibiting CDK2 has been identified as a possible means of treating and/or preventing cancer.

Gunaje and his team confirmed that aspirin and salicylic acid decreased cyclin A2 and CDK2 levels in lung, colon, prostate, ovary and skin cancer cells. They then tested the hypothesis that salicylic acid binds to CDK2, thus interrupting the cyclin A2/CDK2 interaction and therefore halting cancer cell reproduction.

His recent results showed that several salicylic-acid derivatives bind to CDK2 enzymes and significantly inhibit the enzyme function, providing a basis for the development of new CDK inhibitors. "We are excited about this discovery," Gunaje said. Identifying and developing these new anti-cancer drugs will have a significant impact on preventing cancer and improving human health.

Above: Gel electrophoresis is used to analyze how salicylic acid and its metabolites affect proteins that regulate cell division.
Below: Doctoral student Rakesh Dachineni and associate professor Jayarama Gunaje examine data on the inhibitory effect of salicylic acid and its derivatives on cyclin-dependent kinase activity.

OUTLOOK

Problem-solving, cornerstone of SDSU research

American philosopher, psychologist and educational reformer John Dewey said, "a problem well put is half solved."

Discovering solutions is the cornerstone upon which this land-grant institution's research mission is based. This publication features the work of scientists and engineers who seek to improve human health, treat and prevent diseases, and protect the nation's food supply.

As associate professor Stephen Gent puts it, "We are trying to answer really tough questions while also being responsible as we work through them." The data from his computational fluid dynamics models help Sanford Health vascular surgeon Patrick Kelly and his product development team assess the quality of blood flow through new stent graft designs. Gent is our first mechanical engineering faculty member to do this type of research.

Three stories highlight accomplishments made through South Dakota's BioSystems Networks and Translational Research (BioSNTR), a collaborative center established in 2013 through a South Dakota Experimental Program to Stimulate Competitive Research National Science Foundation RII Track 1 award designed to build infrastructure and support research on human, animal and plant diseases.

Through BioSNTR, researchers from South Dakota State and the University of South Dakota are investigating how antibodies recognize their targets, activate immune cells and clear influenza from the body. BioSNTR scientists have also been instrumental in establishing a genome-sequencing laboratory and building faculty expertise in bioinformatics that helps make sense of these large datasets.

To help individuals at risk for developing cardiovascular disease and diabetes, associate professor Moul Dey led the first study to examine the prebiotic impact of a nondigestible wheat fiber for individuals with metabolic syndrome. In addition, associate pharmaceutical sciences professor Jayarama Gunaje is identifying the molecular mechanism through which a daily dose of aspirin reduces a person's risk of developing cancer, particularly colorectal cancer.

Working with Avera Health, Mary Minton and Mary Isaacson surveyed nurses about their comfort levels and techniques used to guide terminally ill patients through palliative and end-of-life care planning. They hope to integrate those strategies and communication techniques into the nursing curriculum and professional workshops.

And finally, researchers at the South Dakota Animal Disease Research and Diagnostic Lab are assessing the pathways through which foreign animal diseases, specifically swine viruses, might reach the United States.

As Dewey pointed out, the enthusiasm and dedication with which our scientists and engineers tackle these problems set them on the path to discovery. That spirit drives research at this university.

Kinchel Doerner, Dean of the Graduate School
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This publication is published by
University Marketing and Communications,
South Dakota State University
Brookings, S.D. 57007-1498.

Fluid flow model evaluates clotting risk in

NEW STENT GRAFT DESIGN

Stephen Gent

Whether patients with mechanical heart valves and stents must take blood thinners depends on how effectively blood flows through these implantable medical devices. Researchers have modeled the flow of blood through left ventricular assist devices and mechanical heart valves to estimate clotting risk, but this type of work has not been done on stent grafts—until now.

Associate mechanical engineering professor Stephen Gent collaborated with Sanford Health vascular surgeon Pat Kelly and biomedical engineer Tyler Remund to evaluate whether a new branching stent design might increase the risk of blood clots.

"An orderly straight-through flow is optimal," said Gent, who has done computational fluid dynamic modeling of stent grafts for the Sanford team since 2014. This work builds on a previous model that provided supporting evidence for well-developed blood flow through a similarly designed stent, which is now part of a Food and Drug Administration-approved investigational device exemption, or IDE, clinical trial.

The results of these projects are published in the Journal of Vascular Surgery. Both projects were made possible through grants from Sanford Research.

Providing options for patients

Only a small number of patients—two per 100,000 a year—are diagnosed with thoracoabdominal aneurysms, according to Kelly. However, most of those patients would not survive traditional open surgery, which involves an incision from the shoulder blades to the groin. The flexible, branching stent grafts that Kelly designs may provide a less invasive alternative.

Of particular concern, was the flow through a section of the branching stent graft where the blood from the main channel, or aorta, branches to the celiac artery, superior mesenteric artery and renal arteries which transport blood to vital organs, according to Remund. "The FDA wants to make sure that you've assessed the risk-benefit ratio and addressed as many risks as possible."

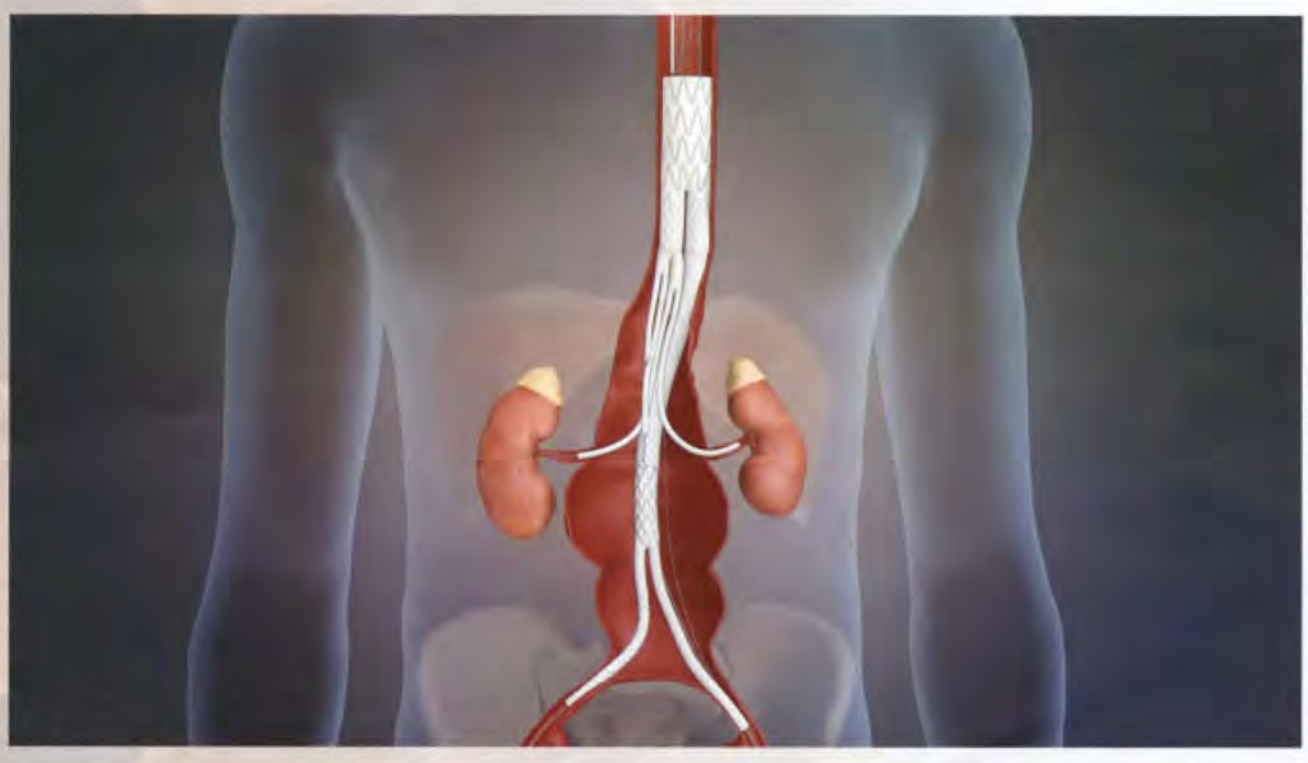
The researchers incorporated aspects of a flow model designed to assess the likelihood of clots forming in mechanical heart valves into their stent graft model. Then they compared the results with those from two mechanical heart valves and an idealized aorta.

Evaluating risk of clotting

"As we expected, Kelly's design performs an order of magnitude lower than was reported for the mechanical heart valves, both of which are FDA-approved for IDE clinical trials," said Gent, who is the first mechanical engineering department faculty member to do this type of research. Furthermore, the blood flow through the stent graft was comparable to that of the idealized aorta.

"Vascular surgeons want the flow to be laminar, so it does not induce turbulence," Gent said. When the blood flows becomes more disturbed, this induces more shear stress on the platelets in the blood. Over time this shear stress, also known as shear accumulation, can damage or activate platelets that can cause them to form clots. These

This proposed prototype for a stent graft designed by Sanford Health vascular surgeon Pat Kelly makes use of a diaphragm where the flow is diverted from the aorta to each of the branch vessels. Computational fluid dynamics modeling to assess the risk of blood clots forming showed blood flow through this stent graft is comparable to that of an idealized aorta.



This illustration shows a stent graft that Sanford Health vascular surgeon Pat Kelly designed and placed within a patient who has a bulging thoracoabdominal aneurysm. Using computational fluid dynamics modeling, associate professor Stephen Gent works with biomedical engineer Tyler Remund, a member of Kelly's product development team, to evaluate the manner in which blood flows through stents, such as this one. A Sanford Health animation showing how such a stent graft is placed within a patient can be viewed at **www.youtube.com/watch?v=sEfHnrjzwIk.**

clots can break off and go downstream where they can easily block blood flow to vital organs, such as the stomach and liver. This is known as thromboembolism formation.

"We are tracking representative blood particles to determine the likelihood of platelets becoming activated," Gent said.

The industry is trying to come up with standardized methodologies and a consensus among experts about what an acceptable set of boundary conditions should be for blood flow through branched stent grafts, according to Remund.

"While developing this model, we were able to study how others approached devices, such as left ventricular assist devices, that are known to activate platelets," he said. LVADs are pumps that can support the blood circulation in patients with severely weakened hearts and consequently tend to create a lot of shear effects on the blood.

"As we continue to push the envelope as an industry, we want to make sure we are not creating unforseen problems for patients," Remund said.

Gent said, "We are expanding our portfolio of capabilities to evaluate these stents for various types of relevant parameters. We are trying to answer really tough questions while also being responsible as we work through them."

Remund added, "Our next focus will be to create benchtop models which can validate our input assumptions for the computer simulations."

"We are trying to answer really tough questions while also being responsible as we work through them."

—Stephen Gent,
associate professor
mechanical engineering

Sanford research project inspires graduate student

When John Asiruwa came to Brookings in fall 2015 to begin graduate work in mechanical engineering, his first stop was the office of associate professor Stephen Gent.

"I want to be involved in something that can make life better for others," he recalls telling Gent. The Nigeria native credits Gent and his work with Sanford Health for igniting his passion for biomedical engineering.

"Dr. Gent and Sanford Health gave me the opportunity that I needed," said Asiruwa, who will complete his master's degree with an emphasis in biomedical engineering this year.

Asiruwa, who earned his bachelor's degree in mechanical engineering from the University of Benin, Nigeria, worked as a process engineer for a year before deciding to go to graduate school. His uncle Christopher Igbinedion, who earned his master's degree in civil engineering here in 1993, recommended his alma mater.

Gent commended Asiruwa for his initiative and enthusiasm: "I have been quite impressed with John's abilities—he is an asset for our research group."

For his thesis work, Asiruwa is using computational fluid dynamics modeling to evaluate how the angle at which the coronary artery branches affects the blood flow and, therefore, the likelihood of clotting and plaque buildup, known as atherosclerosis. This information is vital when carrying out coronary bypass surgeries and placing stents.

"A stent is difficult to deploy in a coronary artery," he explained, noting the critical role that blood pressure and flow dynamics play in this part of the body.

"The takeoff angle of the left coronary artery makes a difference," Asiruwa said. Based on these analyses, he hopes to identify which angles are associated with an increased likelihood of blockages reoccurring. The results will give surgeons data to make decisions that will affect patient outcomes.

"Understanding the flow dynamics in coronary stenting and its complexity will help those designing biostents and tissue-engineered degradable stent grafts for more complex aneurysm-prone regions with delicate arterial networks," explained Asiruwa. He plans to pursue a doctorate in biomedical engineering and hopes to continue doing research on Sanford Health projects.

"I come from an area of the world where minimally invasive medical techniques are not common," he noted. "I feel I am in the right place. I can see what I am doing can be life changing for patients."

Mechanical engineering graduate student John Asiruwa diagrams the branching of coronary arteries. The Nigeria native, who is studying biomedical engineering, is modeling blood flow to evaluate the likelihood of clotting and plaque buildup in the arteries, known as atherosclerosis.

Experience

key to nurses' comfort in communicating with terminally ill patients

Deciding how terminally ill patients want to live—and die—can be complicated. Nurses experienced in palliative and end-of-life care can guide patients and their families through this difficult process, according to associate professor Mary Minton, associate dean of the graduate nursing program.

Minton and assistant professor Mary Isaacson surveyed nurses working in rural and urban settings to assess their comfort levels and document the strategies they use to communicate with these patients and their families. The research was conducted in collaboration with Avera Health and funded through a one-year, $15,000 grant from the Hospice and Palliative Nurses Foundation.

"We are operating against a backdrop of a health-care environment that is more focused on a cure model," Minton pointed out. "We have to embrace the 'letting go' of interventions—that it's OK to do that. This 'letting go' segues to concerns regarding stewardship of health-care dollars."

The nurse-researchers developed and tested an assessment tool called C-COPE, Comfort with Communication in Palliative and End-of-Life Care, and invited nurses at six Avera Health facilities in eastern South Dakota—four rural and two urban—to complete the online survey. Of the 750 to 1,000 registered nurses at these facilities, 277 responded, ranking their comfort level on facets of palliative and end-of-life care communication ranging from physical symptoms to cultural and religious concerns.

Greater comfort level among rural nurses

Overall, the respondents reported what Minton termed "a fair amount of comfort." Individual scores ranged from 26 to 106, with a lower score associated with a higher comfort level, and an average score of 47.9.

Rural nurses, in general, were more comfortable guiding patients through palliative and end-of-life care planning than their urban counterparts. "That makes perfect sense, given the proximity in which nurses live and work in these rural areas—they are integral to that community," said Isaacson, who worked as a nurse in a rural setting.

"Research shows that patients are waiting for their health-care providers to initiate these discussions," noted Isaacson. "Nurses need to have the ability to initiate these crucial conversations and be comfortable talking to patients and families."

Minton continued, "Nurses are in a position to provide a safe, nonthreatening atmosphere where patients can set goals and make decisions about their care. They spend more time with patients and are usually more involved in end-of-life care."

In 2012, only 25 of South Dakota's 14,762 licensed nurses were certified in palliative and hospice care and they tend to practice in an urban setting, Minton explained. Of those surveyed, nurses with specialized training of any kind had a slightly greater, though not statistically significant, comfort level in three areas—delivering difficult news, dealing with spiritual or religious concerns and discussing end-of-life decisions.

Techniques learned through experience

The researchers then interviewed five rural and five urban nurses who had an average of eight years' experience in home health and hospice care to identify the communication strategies they use in guiding patients and their families in end-of-life decision-making.

"What we found is that their techniques were constantly evolving—there was not a linear method," Minton said. "The amount of dexterity these nurses have navigating these situations speaks to how at ease they are—they do not question what they do."

However, the nurses agreed that nothing in their undergraduate education prepared them.

"As new nurses, they could not communicate like this," Isaacson said. They developed these skills through experience, relying on the more seasoned nurses or other health-care professionals as role models.

Five main themes emerged from this qualitative portion of the study. First, the nurses established the context by asking the patients, "What do you know about your illness—where did you start and where have you been?" These nurses want to "hear where the person thinks he's at and work from there," Isaacson reported.

Second, nurses said they listened attentively to what these patients and their families had experienced. "They acknowledged not only the physical and financial losses but also the psychological ones—the loss of dignity because of therapies," Minton explained. "We know these conversations are important, but it's also imperative to be comfortable with silence."

Third, through the education process, the nurses build a trusting relationship with their patients allowing them to understand and prepare for death, according to Minton. "The patients know they are not alone and that their wishes will be honored."

Fourth, the surveyed nurses understand advanced-care planning and end-of-life decision-making, more specifically, "the patient and families' wishes and goals of care. These nurses knew when they had to be frank," Isaacson said. They posed questions such as "Is there something you need to accomplish before you die, while you are still physically able?"

Finally, honesty was interwoven throughout their conversations with patients and families. The nurses often stated that repetition and "presenting reality" were essential, Minton said. "These nurses can be truthful without being apologetic."

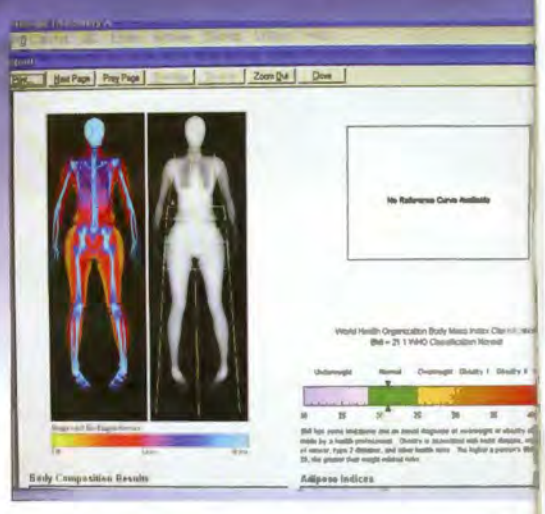
Integrating these strategies and communication techniques into the nursing curriculum and professional workshops is essential to providing competent end-of-life care.

Mary Minton

Mary Isaacson

Nondigestible starch feeds gut microbes, reduces inflammation

Moul Dey



Americans struggling to lose weight often resort to a low-carbohydrate diet, but a newer food ingredient, known as resistant starch type 4 or RS4, may allow them to add some bread products back into their diets while also improving their health, according to Moul Dey, associate professor in the Department of Health and Nutritional Sciences.

RS4, a nondigestible, chemically modified wheat fiber, works as a functional fiber with prebiotic properties, explained Dey, whose research group studies the role of biologically active dietary components in chronic diseases. Unlike simple carbohydrates, which are broken down into sugars in the small intestine, RS4 resists digestion and passes into the large intestine.

"Gut bacteria use it as fuel, releasing beneficial compounds, such as short-chain fatty acids, that are generally believed to keep you healthy. Since RS4 isn't digested, we absorb fewer calories from foods that are high in this type of carbohydrate," Dey said.

Other researchers have studied RS4 in healthy adults, but Dey and her team are the first to examine the impact of RS4 in mitigating metabolic syndrome, which affects one-third of American adults. The combination of high blood pressure, high blood sugar levels, high cholesterol and abdominal fat make those with metabolic syndrome three times more likely to have a heart attack or stroke, and five times more likely to develop Type 2 diabetes, according to the International Diabetes Federation.

The research was supported by MGP Ingredients, the National Institutes of Health and the U.S. Department of Agriculture through the South Dakota Agricultural Experiment Station and involved collaboration with U.S. Food and Drug Administration scientist Ali Reza Fardin-Kia.

Other SDSU collaborators were assistant professor Lacey McCormack from the Department of Health and Nutritional Sciences, associate professor Howard Wey from nursing, professor Jeffrey Clapper from animal science and professor Bonnie Specker, director of the E.A. Martin Endowed Program in Human Nutrition.

Four peer-reviewed articles have been published on their findings since 2014. Two doctoral students, one master's degree student and a postdoctoral researcher worked on the RS4 research.

Improving symptoms of metabolic syndrome

The human clinical trial study involved adults from two Hutterite colonies in eastern South Dakota. Typically, Hutterite diets are high in protein, fat, cholesterol and salt and low in fiber compared to the recommended dietary allowance, Dey noted. Of the 83 participants who completed the trial, 40 had metabolic syndrome and most were on prescription medications for one or more of those conditions.

Unlike most dietary intervention studies, the researchers used a free-living, community-style environment and made minimal modifications to the participants' habitual diet. The intervention was blinded, meaning the participants did not know if they were consuming the RS4 or the control flour at a given time, Dey explained. "Blinding was possible because the neutral sensory properties of RS4 make it undetectable in foods."

RS4, which is currently available only to food manufacturers, was incorporated into the intervention group's flour. All meals in this communal setting are prepared from scratch and every meal contains one or two flour-based items.

The intervention was conducted in two 12-week sessions with a two-week hiatus. This allowed researchers to switch the intervention and control-diet groups so that each group served as its own control. Stool and blood samples were collected and a DXA scan to evaluate body composition was done before and after the intervention.

Use of resistant starch decreased all types of cholesterols, Dey reported. The participants' baseline cholesterol levels were not high, in part, because of the medications they were taking. Despite that, the participants' average total cholesterol dropped significantly after the intervention. In addition, the researchers observed a small but significant decrease in average waist circumference and body fat percentage. Markers of inflammation in blood were lowered as well.

DNA analysis of stool samples using next-generation sequencing showed that RS4 can improve bacterial composition, according to Dey. "Changes in the gut microbial community correlated with improved indicators of metabolic health as well as increased short-chain fatty acids."

In particular, commonly regarded good bacteria, like Bifidobacterium adolescentis, Parabacterium distasonis and the newly described species, Christensenella minuta, increased in response to consuming 9 grams, or approximately 0.3 ounces, of RS4 per day for 12 weeks.

Examining inflammatory gene expression

Some of the inflammation-lowering effects of RS4 found in humans were also confirmed through a mouse model study. The researchers found that butyrate, one of the short-chain fatty acids produced by the gut bacteria, increased in mice fed a diet supplemented with 20 percent RS4 for 12 weeks. Results were published in the September 2016 issue of Food and Function.

"Everyone is born with a genetic blueprint that rarely changes during their lifetime, but diet and environment can epigenetically change how genes function without changing the genetic code," she said. Other researchers have shown that higher levels of butyrate translate to a healthier bowel and a lower risk of inflammation. "We observed that butyrate-induced suppression of pro-inflammatory genes was accompanied with a specific type of epigenetic change that was not shown before," Dey said.

"Our research shows that potentially tailoring a more healthy diet that also tastes familiar and good is possible," she concluded.

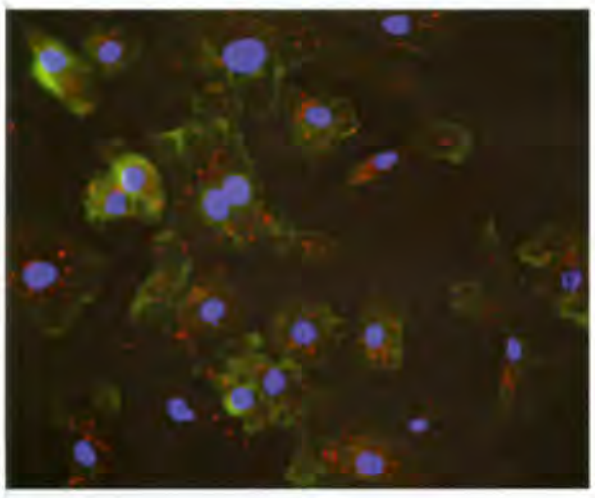
This is critical to mitigate some of the long-term dietary compliance issues often faced by public health promotion programs aiming to curtail the rising trend in obesity and metabolic diseases.

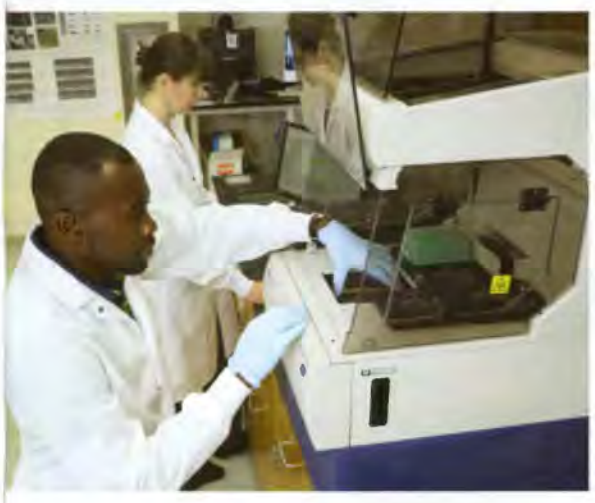
From top: Resistant starch type 4, a nondigestible, chemically modified wheat starch, in the container directly below the bread, has neutral sensory properties that make it undetectable in foods. One of the samples on the right has it, while the other does not.

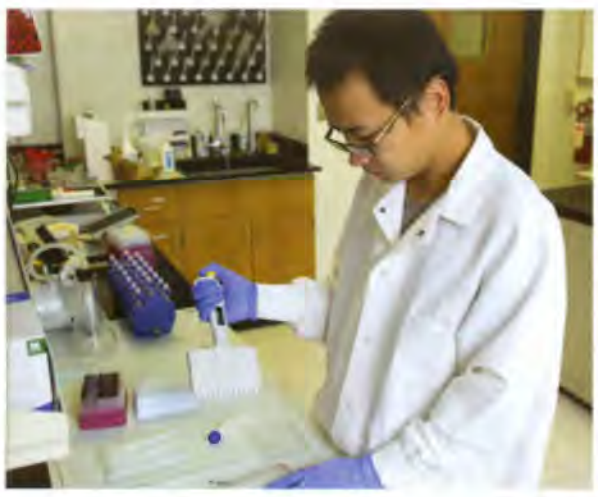
A DXA scan of each participant before and after the intervention allows researchers to evaluate changes in body composition.

Associate professor Moul Dey and master's degree student Robert Juenemann review test results that assess the proinflammatory proteins in the bloodstream of study participants.

Dey, doctoral candidates Bijaya Upadhyaya and Yi Liu and postdoctoral researcher Sailendra Nichenametla examine human colon cells treated with short-chain fatty acids, which helped reduce inflammation.







From top: This microscope image shows immune cells, in green with blue nuclei, that have internalized H1N1 viral particles. Those in red are responding to the therapeutic antibody SAB100. These images allow the researchers to assess how effective different antibodies are at mediating clearance of viruses by immune cells.

Doctoral student George Opoku-Kusi and postdoctoral researcher Svetlana Kurilova use high-throughput microscopy to study how immune cells clear influenza virus from the body.

Using a flow cytometer, research associate Jason Kerkvliet measures populations of single cells to determine how they recognize the antibody therapeutic.

To determine the specific antigen site to which the therapeutic antibody binds, doctoral student Rongyuan Gao prepares an antibody solution, which is part of an enzyme immunoassay to detect and measure which influenza antigens the antibody targets.

Researchers investigate workings of antibody therapeutics

Feng Li

Adam Hoppe

When it comes to emerging viruses, such as a new strain of influenza, antibody therapeutics can save lives. They can be developed quickly and used to rapidly eliminate the virus from an infected person's body.

However, how to make the best therapeutic antibodies is not very clear, according to professor Feng Li. The virologist is part of a team of BioSystems Networks and Translational Research (BioSNTR) researchers investigating how antibodies protect the body from influenza virus. The collaborative project, which began in June 2015, looks at how the antibodies recognize their targets, activate immune cells and clear influenza from the body.

Cell biologist Adam Hoppe, BioSNTR director and associate professor at SDSU; immunologist/virologist Victor Huber, an associate professor at the Sanford School of Medicine of the University of South Dakota; and Li are evaluating and coming up with new ways to predict the efficacy of antibody therapeutics produced by Sioux Falls-based SAb Biotherapeutics (SAB). The biopharmaceutical company's immunotherapy platform was recognized by the World Health Organization as a one of the top platforms for rapidly responding to infectious disease outbreaks.

Huber's research focuses on understanding host antibody responses that are associated with vaccine-induced protection against influenza viruses. A BioSNTR seed grant to perform initial trials on an influenza therapeutic helped SAB and Huber secure a Small Business Innovation Research Grant from the National Institutes of Health last fall to advance its treatment for influenza.

"BioSNTR creates an opportunity to bring components of biomanufacturing—including antigen development—to the state of South Dakota," said SAB president and CEO Eddie Sullivan. "BioSNTR scientists have the refined skills and advanced capabilities to help us develop laboratory tests to show that our antibodies are effective."

Delivering protection quickly

"A vaccine mimics the primary viral infection and, thus, stimulates the immune system to generate antibodies," Li said. That produces what is known as an immune memory, but that takes from a few weeks up to a year. When a patient receives a yearly flu shot, it then reactivates that memory and causes new antibodies to be produced that protect against current strains of influenza.

"In contrast, antibodies can induce an immune response quickly or they can be used in a preventative way," Li said. The antibodies will block any recognizable viruses and can be used during an outbreak, either before or after the patient is exposed. The antibodies live in the bloodstream anywhere from several weeks to several months.

"Antibodies are only temporary, but sometimes temporary can be critical," Li continued, referring to an influenza pandemic or Ebola outbreak. For those with weakened immune systems, such as the elderly, or those with immunosuppressive diseases, such as HIV, antibody therapeutics may be their only viable option.

As part of the BioSNTR team, Huber, who has been doing influenza research since 1997, makes the influenza vaccines, which SAB then uses to generate the antibodies from which the therapeutics are made. He then utilizes a ferret model to test the effectiveness of the end product.

"This allows us to work out the dynamics of the therapeutics," he said. That includes the timing and duration of the injections, as well as the dose needed to produce a protective response.

"We know how much antibody is needed to get protection against influenza from a vaccine, but that amount from a therapeutic is not known," Huber noted.

Unraveling inner workings

"We are helping them figure out the protective mechanism of the antibody," Li explained. "To be effective, the antibody must recognize the virus and then send the immune system to kill the virus."

Li's group uses a molecular approach to figure out where the antibody binds. The surfaces of influenza virus particles have numerous copies of spike-like projections, known as antigens, which the antibodies recognize and adhere to, essentially marking them for destruction by the immune system. Two doctoral students and research assistant professor Dan Wang work with Li to map the specific antigen sites, which the antibodies target.

Because the vaccines used to produce the antibody therapeutics cover multiple strains, the number of antigens to which the antibodies bind indicates the range of the immune response. Huber said, "Inducing a broad immune response will help make a better product."

Hoppe's group focuses on what's happening at the cell level—how the immune system recognizes the antibodies attached to the virus and then clears the virus from the body. One doctoral student is working on this project.

Immune cells, such as macrophages and dendritic cells, have Fc-gamma receptors that recognize the antibodies attached to the virus. The macrophages and other specialized immune cells then ingest and destroy the virus.

In addition, the virus also invades body cells and begins producing more virus. When that happens, the viral proteins, or antigens, appear on the cell surface, Hoppe explained. Antibodies detect these and attach to the infected cells. Through the Fc-gamma receptors, the macrophages and natural killer cells recognize the attached antibody and kill the infected cells.

To understand how the immune cells clear the antibody-coated viruses and antibody-recognized infected cells from the body, Hoppe said, "We develop assays to measure how well the antibody mediates this clearance process."

Though antibody recognition is diverse, Huber noted, "There are only a handful of ways the host eliminates pathogens." His lab works on the whole antibody in relationship to the Fc-gamma receptors.

"We are looking for ways to optimize those interactions to clear the infection more rapidly, especially in the case of a severely infected individual," he added.

What the BioSNTR researchers learn will not only help SAB improve its influenza therapeutic, but also result in technologies that other biotechnology companies can use to evaluate product effectiveness.

DNA, RNA

sequencing available on campus to researchers statewide

Jose Gonzalez

To determine what mechanisms help perennial plants survive the winter or how cancer triggers uncontrolled cell growth, scientists must look within an organism's genetic code. To figure out what is happening, many university researchers must send their samples to large sequencing facilities and wait, sometimes months, for results.

That is no longer necessary at South Dakota State University.

Instrumentation that can sequence the entire genome of an organism is now available on campus, thanks to funding from the National Science Foundation, Agricultural Experiment Station, SDSU Division of Technology and Security and South Dakota's BioSystems Networks and Translational Research (BioSNTR) Center.

"Having a sequencing center in South Dakota allows researchers to rapidly acquire genomic data, conduct bioinformatics analyses and then refine their experimental designs," said BioSNTR Director Adam Hoppe.

"High-throughput genome sequencing is not an option anymore—this is something researchers have to do to get funded," said Department of Agronomy, Horticulture and Plant Science associate professor Jose Gonzalez, who led the team that secured funding.

Gonzalez and department colleagues assistant professor Sunish Sehgal and associate professor Senthil Subramanian as well as biology and microbiology professor Heike Bücking were awarded a three-year, nearly $350,000 NSF equipment grant in fall 2015. The Agricultural Experiment Station and the SDSU Division of Technology and Security provided an additional 30 percent in matching funds.

Gonzalez oversees the genome sequencing laboratory at the Young Brothers Seed Technology Laboratory, which houses the Illumina NexSeq 500 nucleic acid sequencer along with accompanying instrumentation to prepare samples. The lab offers fee-based sequencing services to researchers at universities and biotechnology firms. Since opening last summer, more than 150 samples have been sequenced.

Suited to researchers' needs

"We have a full suite of instruments," Gonzalez said, noting that this model was chosen because "it fits the amount of output that a typical project needs." Through support from the Department of Agronomy, Horticulture and Plant Science and BioSNTR, the researchers also hired a full-time technician, Michaellong Tran, to prepare samples and do the sequencing.

"We can do a run for one single project," Gonzalez pointed out, which means faster turnaround times. "Having a facility here also makes it easier to adapt this technology for investigators who are not familiar with sequencing."

The machine has the capacity to do one or two human genomes in a single run, with an estimated run time of 30 hours. However, plant genomes can be larger than human genomes, Gonzalez noted.

As the SDSU winter wheat breeder, Seghal said the next-generation sequencing facility "will increase the precision in gene transfers. It will help us develop genomic prediction models so that we can deliver better genetics and varieties to South Dakota producers."

Analyzing gene expression

"We can sequence DNA or RNA," he said, noting that there is more demand for the RNA sequencing option. "RNA represents all of the genes that are being expressed at any given point in time and in any given tissue—the working machinery."

For example, a researcher can grow one plant in normal soil and another in high salinity soil and then look at the differences in gene expression between the two plants. "You might have only a few hundred genes differentially expressed—some are the cause of the difference, while others are the effect of that difference," he explained. "That gives you a good point from which to start."

Researchers then combine their findings with other evidence or data to get a better understanding of what's happening. "Nothing gives you a magic solution in science," Gonzalez noted.

"The infrastructure and collaboration that has been made possible through BioSNTR have given my research group new tools to identify the genes involved in soybean nodule development," Subramanian said. His research aims to increase the nitrogen-fixing power of soybeans.

Specifically, Subramanian's research group is examining which microRNAs direct gene expression when pre-existing root cells are transformed into two distinct regions—one that fixes nitrogen and the other that transports it to the plant. For this NSF project, the research team needed to optimize new methods for construction of gene expression libraries from a small number of cells.

The availability of in-house sequencing enabled graduate student Sunita Pathak to customize available methods and select the most efficient one for constructing gene-expression libraries.

Through funding from the Sun Grant Initiative, Gonzalez and his collaborators will sequence the full prairie cordgrass plant genome. "To my knowledge, this will be the first complex genome sequenced all in-house in South Dakota," he said. Prairie cordgrass is a potential feedstock for biofuel production.

"It's more than efficiency," Gonzalez noted. "It's actually allowing us to do things we couldn't do before. It's as simple as that."

From top: Research associate Michaellong Tran loads reagents into a programmable pipetting machine that extracts DNA from samples.

Having an in-house genome sequencing facility shortens turnaround time for SDSU researchers identifying the genes involved in soybean nodule development.

Tran analyzes a sample to check for DNA/RNA fragment size and quality.

Tran and associate professor Jose Gonzalez examine settings on the genome sequencer.

From top: This bulb-like section shows that this grapevine has been grafted, meaning the root system is genetically different from the top portion that produces the stems, leaves and fruit, referred to as the scion. QUBIC-R will help unravel the genetic interactions taking place. *Photo courtesy of associate biology professor Allison Miller of Saint Louis University*

QUBIC-R analyzes RNA datasets from switchgrass (center) and Arbidopsis, a small flowering plant (bottom), faster than three other popular programs—Plaid, Xmotifs and Quest.

QUBIC-R

software helps researchers model, visualize gene expression networks

Qin Ma

Determining the order of the DNA nucleotides—adenine, guanine, thymine and cytosine—that make up an organism through next-generation sequencing technologies has become commonplace. However, generating that code of life is only the beginning.

Genome News Network compares a genome to "a book written without capitalization or punctuation, without breaks between words, sentences or paragraphs, and with strings of nonsense letters scattered between and even within sentences."

To make sense of these big datasets, scientists partner with specialized statisticians who develop algorithms and software that help researchers decipher what's happening within the code.

That is where the work of assistant professor Qin Ma comes in. He developed software called QUBIC to help analyze RNA gene expression data in 2009 as part of his doctoral work. He completed joint doctorates in operational research from China's Shandong University School of Mathematics and in computational systems biology from the University of Georgia.

Now he's updated the software, increasing its efficiency and adding new visualization capabilities. Ma came to SDSU nearly two years ago as a BioSystems Networks and Translational Research (BioSNTR) faculty member in the Department of Agronomy, Horticulture and Plant Science and holds a joint appointment in the mathematics and statistics department.

Analyzing big datasets

"He develops tools to help life science people make sense of their data more efficiently," explained professor Anne Fennell, who has been doing genomic research on cold-hardy grapes for nearly 20 years. Through a National Science Foundation-funded project, she and Ma will analyze how grafting affects cold-climate grapes. Grapes are commonly grafted, so the root system is genetically different from the top portion that produces the stems, leaves and fruit.

"Plant scientists spend a tremendous amount of time going through these big datasets—anywhere from 2 million to 12 million data points," Fennell explained. "One of the unique features of QUBIC is that it can effectively analyze these large biological datasets."

In analyzing RNA from specific segments of the genetic code, scientists seek to determine what the relationships are among the genes. "Some genes are very tightly connected, while others are not," Fennell pointed out. Traditional clustering looks at the genes under one condition, such as level of expression. However, the relationships are often more complex with patterns changing over time.

Ma's software uses biclustering to identify whether these genes are co-expressed under varying conditions, such as different temperatures, stresses or daylength.

"Using biclustering, we are getting things that are more similar," Fennell explained. Ma added, "Identifying biclustering helps elucidate the overall regulatory system and gene expression network."

Making QUBIC faster

To improve the program's efficiency, Ma implemented the program using R, a computer language that statisticians and bioinformaticians use. That decreased the average run time by 82 percent compared to the previous version, which was coded in the C language, Ma explained. "Efficiency is very important in the big-data era."

To test the software, Ma input data containing 900 million elements and processed them in 30 minutes. "This software is very robust—and can be applied to all kinds of data," added Fennell, including datasets generated by animal scientists, microbiologists and virologists.

QUBIC-R outperformed three popular analysis packages on five RNA datasets—E-coli bacteria, the small flowering Arabidopsis plant, grapes, a human tumor and switchgrass—as detailed in an article the researchers published in the November 2016 issue of Bioinformatics. It is the official journal of the International Society for Computational Biology, the leading professional society for computational biology and bioinformatics.

QUBIC-R is an open access software available free through Bioconductor, one of the nation's largest bioinformatics companies. "Having it on Bioconductor means that it's readily available and being used globally," Fennell said.

Furthermore, Ma pointed out, "You do not have to be a bioinformatician to use this program."

Fennell added, "Even those with not a lot of computational background should be able to easily use the program."

Visualizing relationships, setting up experiments

QUBIC–R also features enhanced means of visualizing gene expression and looking at specific genes within a network. The software not only creates heat maps which show the level of gene expression based on color intensity in identified clusters, but can also generate co-expression networks that visualize the importance of specific genes within those networks.

Researchers want to know, not only how they are connected, but also how strong those connections are, explained Ma. The software allows the researchers to delete data from specific genes and thereby figure out a gene's importance in the biological network.

Using co-expression network, he said, "we can see through the size of the circle (that represents a specific gene) when more interactions are taking place. The thickness of the lines (or connections) also gives you more of the dynamics."

Experiments are designed to test a hypothesis. Therefore, researchers tend to focus on parameters related to their hypotheses. By using QUBIC-R as a computational tool, researchers can do "hypothesis-free" data exploration.

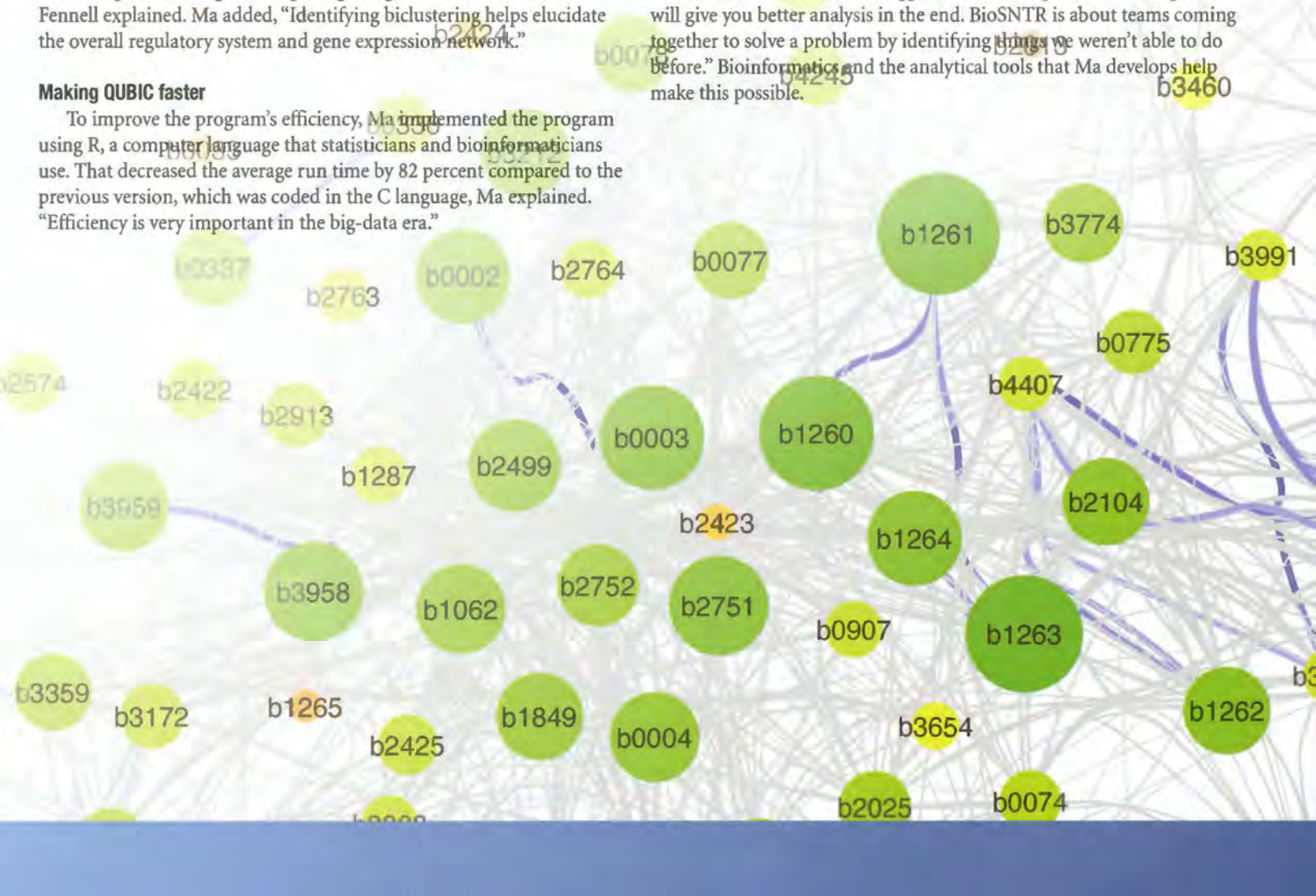
"This type of computational analysis can show you what you might be missing because of that hypothesis-driven focus," Fennell said.

Through his role in BioSNTR, Ma helps researchers design their experiments, determining how many samples to prepare and what kind of sequencing is suitable to test the hypothesis. "It's very important to think computationally when you are developing your experiments," Ma said.

Fennell added, "Qin can suggest tweaks in experimental design that will give you better analysis in the end. BioSNTR is about teams coming together to solve a problem by identifying things we weren't able to do before." Bioinformatics and the analytical tools that Ma develops help make this possible.

At right: The ability to visualize co-expression networks is one of the major strengths of QUBIC-R. The colors identify the interacting groups within the network. The dot size signifies the gene interactions taking place and the connecting line width shows dynamics of those interactions.

QUBIC-R can be downloaded for free using the QR code below.
https://bioconductor.org/packages/release/bioc/html/QUBIC.html



Scientists assess survival of swine viruses in IMPORTED FEED INGREDIENTS

Eric Nelson

Diego Diel

Researchers must use a global perspective to assess the risk that foreign animal diseases pose to the pork industry and the pathways through which these pathogens might reach the United States, according to Paul Sundberg, executive director of the National Pork Board's Swine Health Information Center.

One of those pathways may be through imported feed ingredients.

Scientists from the South Dakota Animal Disease Research and Diagnostic Laboratory, collaborating with Scott Dee, director of research at Pipestone Veterinary Services in Minnesota, discovered that porcine epidemic diarrhea virus (PEDV) can survive a simulated trip from Beijing, China, to Des Moines, Iowa, in five feed ingredients. The study was funded by the National Pork Board. Their results were published in BMC Veterinary Research.

Those findings led to a subsequent project exploring whether 10 other viruses might also survive the transglobal journey. The study began in March 2016 and is supported by the Swine Health Information Center, which began operation in 2015.

"We need to be better at being able to manage emerging diseases because they are going to happen," Sundberg said. Headquartered in Ames, Iowa, the center monitors foreign pathogens to help veterinarians and producers respond to emerging diseases.

Identifying viability of PEDV in feed ingredients

"When PEDV broke out in 2013, there was some suspicion that feed was involved in some manner, but we didn't know for sure how that could happen—we had no data," Sundberg said.

In January 2014, sows and gilts in three herds on farms with high biosecurity levels came down with PEDV. "These were very biosecure farms that were free of PRRS (porcine reproductive and respiratory syndrome) and other viruses for many years," Dee said. "It was like someone flipped a switch and the commonality was an emergency feed outage."

Dee worked with ADRDL director Jane Christopher-Hennings and professor Eric Nelson to prove that contaminated feed triggered the outbreaks. They then investigated whether the virus could survive in 14 ingredients that are commonly shipped to the United States from China.

The researchers used an environmental chamber, which Pipestone Veterinary Services purchased and donated to ADRDL, to replicate the environmental conditions in shipping containers during the 37-day journey from Beijing through the port of entry in San Francisco to Des Moines. The temperatures and relative humidity simulated a Dec. 23 through Jan. 28 trip, a timeline associated with the April PEDV outbreak.

Results showed that PEDV can survive the journey in five feed ingredients—vitamin D, lysine, choline and organic and conventional soybean meal. The study concluded that "soybean ingredients can potentially present a considerable risk for transboundary spread of PEDV."

Approximately 7,300 tons of conventional and organic soybeans were imported from China in 2013 and 2014, according to information from the U.S. International Trade Commission Harmonized Tariff Schedule.

In addition, the researchers tested several compounds that could potentially decrease the risk of live viruses in feed.

"This was the first research of this type in the world," Dee noted. "This is a well-coordinated project that is trying to solve real-world problems."

Assessing risks from other viruses

Assistant professor Diego Diel said, "The next logical question is what other high-impact viruses could be potentially coming into the country through contaminated feed ingredients." The virologist leads the team of two research associates and one visiting scientist who are assessing 10 key viruses using the transglobal environmental model.

Diel and Dee worked with Sundberg to select the high-priority animal diseases, three of which are already in the United States—PRRS virus, vesicular stomatitis virus and circovirus. "Viruses from the same family with similar characteristics are used as surrogates for the viruses not present in the United States," Diel said.

The first phase of the project examined Senecavirus A as a substitute for foot and mouth disease virus, bovine viral diarrhea virus as the surrogate of classical swine fever virus and bovine herpes virus-1 for pseudorabies virus. Other diseases for which the group is using surrogate viruses are Nipa virus, vesicular exanthema virus and enterovirus.

"We prioritized the diseases according to the potential impact on domestic and international markets, economic effects on production and likelihood that they could be introduced or, if already in the country, could emerge as a problem," Sundberg explained. About half these diseases have strains that infect other animal species, which gives this study an even broader impact.

In selecting feed ingredients, the researchers focused more on ground ingredients, adding moist dog and cat food, dry dog food and pork sausage casing to the list. "To make it a more diverse list, we looked at what comes into the San Francisco port of entry," Dee said, noting that the U.S. ships pig bladders, stomachs and intestines to China for processing. The sausage casings represent the import of these processed products back into the United States.

Impacting animal health

"This is an extremely important project, one which, to my knowledge, has never been done before in any species. It identifies potential risks to animal health in the United States from importing different products that you might not think could be a risk," Sundberg said.

The experiments will be completed this spring and analyses of results are ongoing, according to Diel.

"We're seeing differences in virus survival across virus types and ingredient types. Identifying those high-risk combinations will be an important outcome," Dee explained. "We will have some powerful stories to tell based on science, not just speculation."

Sundberg said, "The issue comes down to being better prepared for new, emerging diseases and more knowledgeable of the risks."

As Nelson puts it, "The ultimate goal is to protect U.S. agriculture."

From left: These vials contain feed ingredients, such as soybean meal, soy oil cake, dried distillers grain solids, lysine, choline, Vitamin D, moist and dry dog food, moist cat food and sausage casings.

Research associate Aaron Singrey places vials containing feed ingredients into an environmental chamber programmed to replicate changes in the temperatures and relative humidity during shipping from China to Des Moines, Iowa.

Visiting scientist Marcello DeLima adds a buffer to recover virus from the samples.

Suresh Damodaran—Joseph Nelson Graduate Scholarship

Gene linked to hormone that impacts soybean-nodule development

Suresh Damodaran, a doctoral candidate in the Department of Agronomy, Horticulture and Plant Science, has been awarded a Joseph F. Nelson Graduate Scholarship for research identifying a gene that is linked to a hormone that affects soybean-nodule development. The scholarship recognizes outstanding graduate students for their original scientific research, providing $2,500 for tuition and fees.

Damodaran's research is part of a National Science Foundation project to identify the genetic mechanisms that direct and coordinate formation of the soybean nodule. Through this project, associate professor Senthil Subramanian hopes to increase the plant's ability to fix nitrogen and thus reduce the need for chemical fertilizers.

"This scholarship is a big motivation for my research and for my future career," Damodaran said. He came to South Dakota State University in 2010, earning his master's degree in plant science December 2012 and then continuing in the doctoral program. He will complete his doctorate in plant molecular biology this year and hopes to find a postdoctoral position working on plant genetics.

"Suresh is very bright, enthusiastic and self-driven," Subramanian said, noting that Damodaran not only conducts his own experiments but also trains undergraduates in plant biology research. "The award is a well-deserved recognition of Suresh's excellent commitment and hard work toward his research goals. It's a pleasure to have him on my research team."

Damodaran praised Subramanian as "an excellent mentor who is always available and open to suggestions. He introduces new ideas every week about research in other labs and encourages us to come up with our own ideas."

Identifying gene expressions

The soybean plant, a legume, interacts with bacteria in the soil to form organs called nodules, explained Damodaran. Within the nodules, two distinct zones—one that fixes the nitrogen and another that transports it to the plant—are formed from the pre-existing root cells. The expression of specific genes in a particular root cell determine its function.

Through their previous studies, Subramanian's group found that the auxin hormone reduced nodule numbers. As part of a large-scale experiment to identify which genes are expressed in the nodule tissue, Damodaran focused on auxin production and identifying the genes regulating auxin levels in the nodules. That quest led him to the SUR2 gene.

"If we consider genes as workers involved in constructing the nodules to determine one particular gene's function, we take that gene or worker out of the system and see how the construction goes," Damodaran said. However, he noted, soybean genes usually belong to huge families. As a result, when one is taken out, another takes its place.

Linking gene, auxin production

When Damodaran reduced the expression of the SUR2 gene, thus increasing auxin production, the plant produced fewer nodules. Conversely, when he treated the plant with a chemical that reduces auxin levels, the nodule numbers increased.

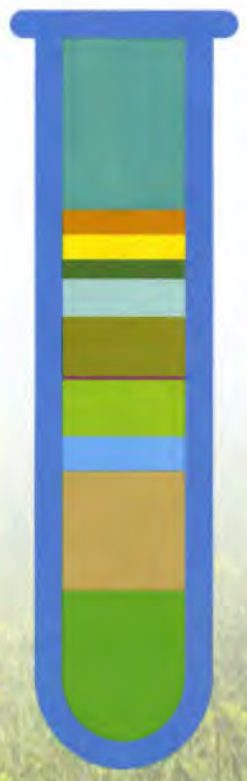
In addition to supporting the group's initial evidence regarding auxin's role in nodule development, Damodaran is the first to report the key role that the SUR2 gene plays in this process.

"This guy is really important," Damodaran said. Plants typically use an amino acid called tryptophan to make other compounds and as a precursor from which auxin is produced. However, he added, "When this gene is suppressed, all the available trytophan flows toward auxin production."

Despite the significance of this finding, Damodaran said, this is just one piece of the bigger model that will ultimately help the researchers optimize overall nodule development.

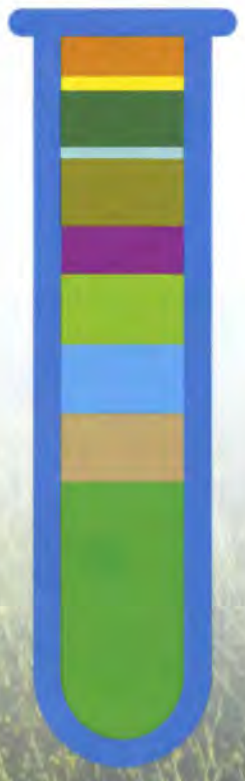
Doctoral student Suresh Damodavan examines soybean seedlings that have been genetically altered. These experiments helped him discover the key role that the SUR2 gene plays in nodule development.

Measuring research investments



Funding source for FY 2016 expenditures through grants and contracts
Total $46,797,995

- Nonfederal
- Other federal
- U.S. Dept. of Education
- U.S. Dept. of Tranportation
- U.S. Dept. of Interior
- NASA
- U.S. Dept. of Defense
- Health and Human Services
- U.S. Dept. of Energy
- National Science Foundation
- U.S. Dept. of Agriculture



FY 2016 expenditures through grants and contracts presented by colleges and research centers
Total $46,797,995

- Others
- Pharmacy and Allied Health Professions
- Arts and Sciences
- E. A. Martin, Human Nutrition
- Geospatial Sciences Center of Excellence
- Education and Human Sciences
- Sun Grant
- EPSCoR
- Jerome J. Lohr College of Engineering
- Agriculture and Biological Sciences

Ag engineering doctoral student develops separation methods for biofuels

Work on two biofuels projects has earned Agricultural and Biosystems Engineering doctoral student Yuhe Cao the Joseph F. Nelson Graduate Scholarship. The award recognizes outstanding graduate students for their original scientific research and provides $2,500 for tuition and fees.

Cao has developed separation methods that will add value to biofuels research aimed at producing jet fuel from camelina and biobutanol from plant materials. The research is supported by the U.S. Department of Energy through the Sun Grant Initiative, which supports the development of renewable, biobased energy technologies, and the South Dakota Oilseeds Initiative.

After earning his master's degree in material processing in 2009 from Tianjin Polytechnic University, Cao worked at a membrane filtration and separation company for four years before coming to South Dakota State to pursue his doctorate.

"I am honored to be one of the scholarship recipients," Cao said. "This will motivate me to work hard and achieve excellence in my research during the rest of my tenure at SDSU and beyond." He plans on completing his doctorate this year and hopes to get a position in academia that allows him to continue research in separation science and technology.

"Yuhe's industrial experience and passion for developing new separation technologies have been integral to his success," said Cao's adviser, associate professor Zhengrong Gu. "His dedication to excellence in research has made him an asset to my team and to this university."

Separating byproducts from camelina

Cao has developed a new method of separating a compound called glucosinolate from camelina, a broadleaf oilseed from the mustard family. Glucosinolate is one of the bioactive compounds that remains after the oil has been extracted, according to Gu. The presence of glucosinolate limits the amount of camelina meal that can be incorporated into animal diets to 10 percent.

"It's very toxic," he pointed out, and it's that toxicity that Gu wants to utilize—to kill fungus and weeds or even cancer cells.

Cao extracts the glucosinolate with ethanol and then uses membrane filtration to remove impurities, such as proteins. Then he uses an ion exchange column to further purify the glucosinolate.

"If we recover it and, at the same time give the solids back to use as animal feed, we have a win-win game," Gu said.

Extracting biobutanol

In addition, Cao also developed a more efficient, less energy-intensive means of separating butanol from the fermentation broth that produces acetone-butanol-ethanol from lignocellulosic biomass. Biobutanol has a higher energy content than ethanol and can be used in conventional gas engines without modifications, according to biobutanol.com.

"One of the main issues in acetone-butanol-ethanol fermentation is that butanol concentrations in the fermentation broth are low, ranging from 1 to 1.2 percent in weight, because of its toxicity to the microorganisms," Cao noted.

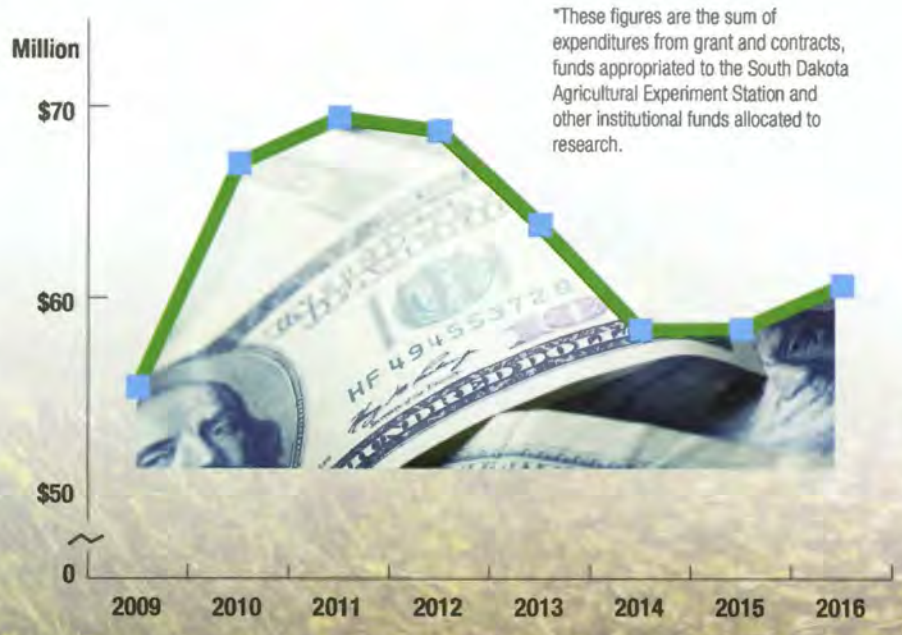
New solid extraction separation methods that add substances, such as polymer resin and zeolite or activated carbon, to the biobutanol fermentation broth to adsorb the butanol can recover only low concentrations of butanol and damage the fermentation microorganisms. Though another new recovery method, known as gas-stripping condensation, improves the fermentation process, it still requires expensive liquid nitrogen.

Cao's process uses helium to do the gas stripping and then a column with activated carbon fabricated from cornstalks more efficiently recovers butanol from vapor stream. Because the method continually captures butanol while preserving the fermentation microorganisms, it recovers butanol in higher concentrations while consuming less energy than traditional methods.

"This is a much more efficient way of separating butanol," Gu said. "It saves lots of energy." The research team has filed an invention disclosure on the helium-based gas-stripping separation method.

Working with associate professor Zhengrong Gu, doctoral student Yuhe Cao, right, carefully inserts a tube loaded with activated carbon fabricated from cornstalks into the chemisorption analyzer. The butanol-recovery process that Cao developed separates more butanol using less energy than other methods.

Total research expenditures FY 2009 - 2016*



*These figures are the sum of expenditures from grant and contracts, funds appropriated to the South Dakota Agricultural Experiment Station and other institutional funds allocated to research.

Research expenditures increase

Overall, FY2016 expenditures through grants and contracts rose by 7.53 percent, approximately $3.28 million, compared to FY2015.

Although the College of Agriculture and Biological Sciences continues to account for a lion's share of research dollars—approximately 38 percent, other colleges have seen large gains in research funding in the last fiscal year. The College of Pharmacy and Allied Health Professions more than doubled its research funding, going from $432,290 in FY2015 to nearly $950,000 in FY2016, while the College of Arts and Sciences experienced nearly a 30 percent increase during that same period.

In assessing changes in the levels of funding by agency, the university had a 45 percent increase in Department of Education funding from FY2015 to FY2016, an approximately 24 percent increase in Department of Health and Human Services funding, a nearly 20 percent increase in NASA funding and close to a 10 percent increase in funding from the National Science Foundation. In addition, for the second year in a row, nonfederal funding increased—this year by nearly 13 percent.

Total FY2016 research expenditures, which include expenditures from grants and contracts and funding appropriated to the South Dakota Agriculture Experiment Station and other institutional funds allocated to research, are up by $2.3 million from FY2015.

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Research enhances undergraduate experience

Undergraduate research in nursing, applied mathematics and cell biology has enriched the academic experiences of three graduating seniors, who shared their findings with South Dakota legislators at the Student Poster Session in March.

Nursing student Lauren Shell looked at how the College of Nursing can better prepare students to address patients' spiritual and emotional needs. She chose an academic-specific project because she is interested in one day becoming a nurse-educator.

Shell identified the need for students to practice what they learn in class with regard to assessing a client's spiritual needs. She concluded that experiential learning and faculty role-modeling would help strengthen this part of the nursing curriculum. In July, she will begin work at Mercy Medical Center in Des Moines.

"We will experience mortality and see hardship in others, but we must learn to meet patients where they are," she added. "It's about being comfortable with the uncomfortable."

Mathematics major Nick Stegmeier altered a fluid-flow simulation program that was part of assistant mechanical engineering professor Jeff Doom's dissertation, making it faster and able to handle slower fluid flows than the original version. Engineers utilize flow simulations to design anything from pipes to jet engines.

"This project is the perfect mix of physics from an engineering standpoint and mathematics," said Stegmeier, who will begin graduate work at SDSU this fall. "It opened up this field to me."

Using macrophages from mouse bone marrow and mouse fetal livers, biology/microbiology major Carson Eisenbeisz examined the proteins that interact when colony-stimulating signaling factor-1, or CSF-1, binds to CSF-1 receptors on the cell surface. This signaling process controls cellular growth.

"This experience has given me an appreciation for the things we do know about biology, the human body and science," said Eisenbeisz, who will attend medical school in the fall. "It has sparked my intellectual curiosity."

Lauren Shell

Nick Stegmeier

Carson Eisenbeisz

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