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Healthy Beginnings

Livestock reproductive research could better human life

by Edith Chenault

Dr. Guoyao Wu's eyes light up as he points to the scientific papers on his desk. His words tumble out of his mouth, faster and faster. He can't sit still; he stands and then sits down. He acts like a new father whose child has just been born.

It's only fitting. The Texas Agricultural Experiment Station animal scientist is part of an interdisciplinary team that has not only been working to solve livestock reproductive problems, but also may help solve the problems of human infertility and underweight newborns. The team's discoveries could also lead to new drugs that treat diseases such as multiple sclerosis.

"We discovered this," Wu says of the explanation of low birth weights in livestock contained in a recent *Journal of Animal Science* article on his desk. "It's very remarkable."

That "we" is Texas A&M's Uterine Biology and Pregnancy Team, made up of researchers and faculty from the Experiment Station, the Texas A&M University Department of Animal Science, and the College of Veterinary Medicine and Biomedical Sciences.

Dr. Fuller Bazer, Distinguished Professor and O. D. Butler Chair in Animal Science, began assembling the team more than 14 years ago. "The team is built on people coming together with a common interest, and people who are excited about their work," he says. Bazer calls Wu "a walking encyclopedia on metabolic pathways and metabolism of amino acids."

Discovery: Spike in protein building block helps placenta and fetus grow

One of the team's goals is to ensure healthy livestock fetuses and offspring. But there's more to it than that.

"Our mind-set is to do research that cuts across both the agricultural and biomedical communities," Bazer says. This means their research has the potential to help both animals and humans.

Approximately 12 percent of U.S. newborns are intrauterine-growth-retardation infants, Wu says. Most are born to mothers who suffer tremendously with morning sickness early in the pregnancy or to teenage mothers who were still growing themselves and were competing with the fetus for nutrients. No cure is available, and these children stay small and suffer numerous health problems later in life, Wu says.

In searching for ways to help pig fetuses grow, the team discovered a spike of arginine, an amino acid and a building block of protein, between Days 30 and 60 of gestation. The arginine spike, combined with oxygen, increases the production of nitric oxide. That causes blood vessels to dilate and grow, increasing nutrient transfer from mother to fetus. "The more nutrients and oxygen that come from the mother, the faster the fetus will grow," Wu says.

This has implications for humans as well, says Wu, because the conversion process is similar. The team hypothesized that

Photo: Jerrold Summerlin

Opposite: By studying normal fetal development in livestock, Texas A&M's Uterine Biology and Pregnancy Team hopes to discover why abnormal conditions occur and how to treat them. This normal bovine fetus and its placental membranes (conceptus) was photographed at about 60 days of gestation. Above: Dr. Guoyao Wu studies the metabolism of amino acids, primarily in pigs. He is excited about the team's discovery of the reason for low birth weights in livestock.

Photo courtesy of Fuller Bazer

Photos: Jerrold Summerlin

intrauterine growth retardation results from reduced placental growth. Their theory has been noted by the U.S. Department of Agriculture's National Research Initiative as a "cover story" —a brief summary of an article featured on the cover of a major scientific journal, in this case the article "Maternal Nutrition and Fetal Development," published in the *Journal of Nutrition*, September 2004. Thomson Scientific's Essential Science Indicators named the article a "New Hot Paper" in January 2006.

Clinical trials conducted in 2005 showed that an intravenous infusion of arginine to pregnant women with intrauterine-growth-retardation fetuses resulted in a 6.4 percent increase in infant birth weight at full term.

Discovery: Sheep interferon tau may help fight multiple sclerosis

In 1977, Bazer published work showing that the hormones estrogen and prolactin cause pigs to recognize that they are pregnant. Later work showed the signaling system in ruminants (sheep, cattle and goats) is triggered by interferon tau, a novel protein produced by the conceptus (the embryo and its associated membranes). The human body normally produces interferons to ward off viral infections.

Interferon tau has great potential for treating viral-based animal and human diseases. One use of ovine (sheep) interferon tau is to prevent viremia (the presence of viruses in the blood) in lambs, he says.

Bazer explains, "When we get a foreign organism in our body, the immune cells mount an immune reaction to kill the organism. However, our immune cells can, in certain diseases like MS [multiple sclerosis], begin to attack [for example] nerve cells and damage them so that they are not functioning properly.

"The other type of immune response is for immune cells to make an antibody against a foreign protein or proteins or an organism, so that we are said to be immunized against the protein or organism."

Interferon tau shifts the immune cell function from killing an organism to producing antibodies, Bazer says. For multiple sclerosis patients, that means the immune system stops attacking nerve cells.

While interferon tau cannot be used to prevent the onset of multiple sclerosis, it can alter the immune system so that nerve cells can recover as much as possible, he says. That allows restoration of function to damaged nerves and, therefore, the patient's ability to regain the use of muscles supplied by those nerves, Bazer adds.

Sheep interferon tau is now in Phase III clinical trials in humans (the final phase before FDA approval) as a treatment for multiple sclerosis, psoriasis, rheumatoid arthritis and hepatitis. The Pepgen Corporation, which licensed Bazer's patent, is testing interferon tau at various sites in the United States.

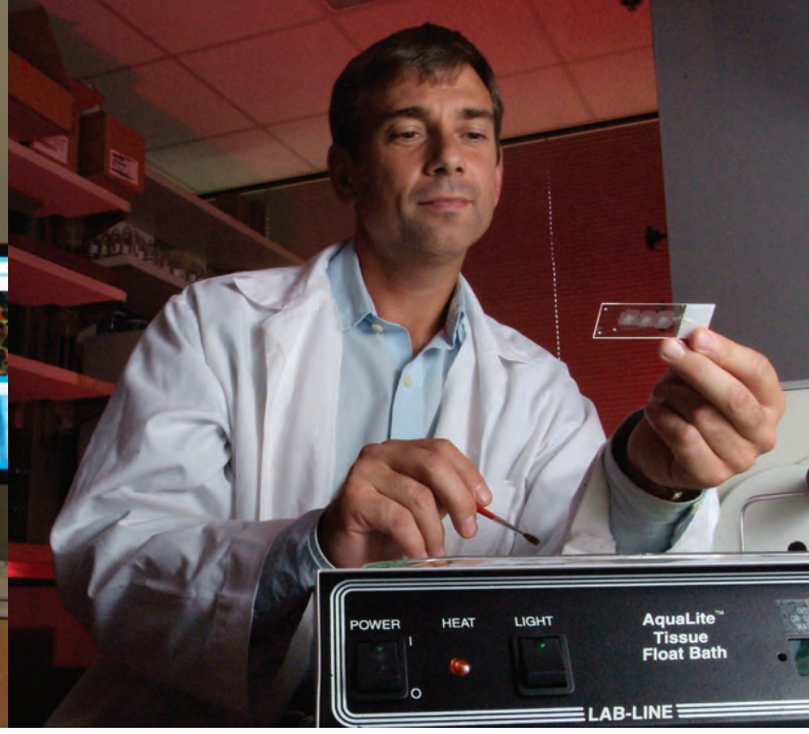
An added benefit is that the protein does not have the debilitating cytotoxic (harmful to cell structure) effects of other interferons that have been used to treat various viral-based and autoimmune diseases, he says.

Research: Studying uterine function in ewes could improve women's health

The team has also been working on "uterine gland knockout" in ewes, which will allow researchers to understand the genes that are important to the development of a normal uterus, Bazer says. In this research, led by Dr. Thomas E. Spencer, associate professor in the Department of Animal Science, lambs are exposed to progesterone, a female hormone, for 56 days from the day of birth. The genes needed for the uterus do not develop normally, and the lambs are unable to have normal estrous cycles or maintain pregnancy beyond 14 days after mating.

This has allowed researchers to compare animals with normal estrous cycles and the ability to conceive to those that

ABOVE, LEFT TO RIGHT: Dr. Fuller Bazer assembled the team. While solving livestock reproductive problems, many of the team's findings can also benefit humans. With Bazer in the lab is Jennifer Farmer, a graduate student in reproductive biology. Understanding genetic responses for reproduction is key to Dr. Tom Spencer's work. He led research that showed uterine genes are not expressed normally when ewe lambs are exposed to progesterone for 56 days after birth.



don't. From this comparison, they have been able to learn much about the hormonal, cellular and molecular mechanisms that regulate uterine gland development and the ability of the uterus to support development of the embryo, fetus, and placental material and fluids in livestock. The researchers hope these types of studies will also lead to discoveries that can be used in medical treatment to reduce fibroid tumors and endometriosis in women, Bazer says.

Discovery: Gene critical for pregnancy also helps defend against viruses

Other work has targeted the cellular and molecular signals that regulate ewes' and sows' ability to become pregnant, maintain pregnancy, and allow the conceptus and the uterus to interact. He says this work may have implications for women who cannot conceive or carry a baby to full term.

The fertilized egg needs a receptive uterus in which to implant and form a placenta. From 25 percent to 40 percent of embryos die, in both humans and livestock, he says, mostly because of the lack of a proper "window of implantation."

In addition to the team's hormonal, cellular and molecular research, Spencer and other researchers found that the gene for an endogenous retrovirus is critical for pregnancy. It also helps the female reproductive tract defend against viral infections during pregnancy, Bazer says.

When viruses attack, they seek to bind to cellular targets, called receptors, within the body. When under attack by a virus, the uterus makes proteins that bind to receptors the virus would normally occupy. Similar to aircraft dropping chaff (tiny bits of metal or glass fibers) to elude radar detection, the proteins block infection by the virus, Bazer explains.

The team's work is at the forefront of pregnancy biology research. Because of the human health connection, most of their projects have been funded by the National Institutes of Health. Others have been funded by the U.S. Department of Agriculture and the U.S.-Israel Binational Agricultural Research and Development Fund. Much of the team's research results in basic information, Spencer says. "But it is often picked up by other researchers and clinicians and used for applied or translational science," he adds.

Team members attribute their success to collaboration. Spencer says the scientists and their students present ongoing research at weekly lab meetings. The team uses these meetings to refine experiment designs and propose new experiments.

"All of us are involved in the training of research fellows, graduate and undergraduate students," says Dr. Robert Burghardt, professor of veterinary integrative biosciences, College of Veterinary Medicine and Biomedical Sciences. "So we have a large educational component built in." Burghardt heads the Image Analysis Lab, which allows the team to analyze cells and tissues microscopically.

"It's a group that thrives on the discovery of new information," says Dr. Greg Johnson, assistant professor in veterinary integrative biosciences. Johnson describes himself as "a ranch kid from Wyoming" who, although he loved biology, never set out to be a scientist. "It is exciting to be the first to see a biological process in the laboratory," he adds.

"We as a team sense where we need to go," Burghardt says. "All of us are collectively focused on the same goal in terms of uterine biology."

In January 2006, the Uterine Biology and Pregnancy Team received a Texas A&M University Vice Chancellor's Award in Excellence for its groundbreaking work.

Joy Pate, professor at The Ohio State University Agricultural Research and Development Center, wrote in her letter of support for the nomination, "There is a momentum in this research team that is going to ensure a high degree of productivity and quality research for years to come."

Above, left to right: The team's Image Analysis Lab, headed by Dr. Robert Burghardt, allows the researchers to microscopically analyze cells and tissues. Dr. Greg Johnson studies a thin tissue section of pig uterus that will provide insight into the physiological processes that govern successful pregnancy. This information can be used to increase reproductive performance in domestic animals and to overcome uterine-derived infertility in women.

Web site:
http://animalscience.tamu.edu/ansc/cabg/index.htm