Public release date: 8-Jan-2004

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Researchers seek to clone 'mad cow disease' resistant cattle strain

Blacksburg, Va. --Scientists in the Virginia-Maryland Regional College of Veterinary Medicine (VMRCVM) at Virginia Tech are trying to clone cattle that are genetically incapable of developing "Mad Cow Disease."

As federal and state government officials grapple with strategies to limit the economic and health risks associated with the troublesome discovery of the nation's first case of Bovine Spongiform Encephalopathy (BSE) – or "Mad Cow Disease"-- Will Eyestone, research associate professor in Large Animal Clinical Sciences, and Bill Huckle, associate professor of biomedical science, are conducting important research with the little understood molecules believed to cause the deadly brain-wasting disease.

Eyestone, a molecular reproductive biologist who was senior research scientist for PPL Therapeutics, the organization that cloned Dolly the sheep, now heads the VMRCVM's transgenic animal research program.

Most people think of disease as being caused by infectious organisms like bacteria, viruses, rickettsia, protozoa or fungi, explains Eyestone. Those microorganisms reproduce themselves to cause disease in fairly conventional ways, either inside a cell or elsewhere in the body.

But prions behave very differently than these more common disease-causing organisms, explains Eyestone. Prions are actually a form of protein that naturally occur in all mammals, though scientists remain uncertain about the exact purpose they serve in advanced mammals like humans. Transmissible spongiform encephalopathies like BSE and new variant Creutzfeldt-Jacob Disease (vCJD), the human form of the disease, are believed to occur when the non-pathogenic prions that normally reside in mammalian nervous systems are converted into pathogenic forms.

Proteins, the building blocks of metabolic processes, are long chains of amino acids that fold in upon themselves in predictable patterns and shapes that result from the bio-electrical relationships that exist between individual molecules, according to Eyestone. Proteins normally "fold" in only one way. But when the "normal" prions are infected by pathogenic prions, they begin to "fold" in another way that leads to disease.

In the case of BSE and vCJD, pathogenic prions introduced from contaminated food sources interact with normal prions in the body and transform them into the lethal agents that eventually create the "Swiss cheese-like" lesions in the brain that cause the devastating neurological symptoms of the disease.

The pathogenic prions that are ingested by cattle in contaminated feed do not seem to be affected by the normal enzymatic activity of the digestion process, explains Eyestone. The prions pass through the wall of the gut and are subsequently absorbed by innervated lymphatic tissues, where they

eventually accumulate in the nerves, and then migrate to the spinal cord and brain. The process takes years, Eyestone says, which accounts for the five to seven year incubation period that characterizes both the animal and human forms of the disorder.

While scientists don't know how to stop the pathogenic process once it gets underway, some, like Eyestone and Huckle, are interested in creating an animal that lacks the genomic architecture to code for the production of normal prions.

"In order to be susceptible to prion disease, the individual has to be able to express the prion," says Eyestone, who is using the same somatic cell transfer technology to clone a cow without normal prions that PPL used to create Dolly the sheep and Mr. Jefferson, the first cloned calf.

Basically, the process involves taking somatic cells harvested from an animal, and replacing the nucleus of that cell with the nucleus of another cell that possesses the desired genetic characteristics, and then implanting that embryo into the animal for a normal gestational development period.

"We know that if you knock out these prion proteins in laboratory mice that there is no apparent negative effect," said Eyestone. "We know that this prion does not appear to be required for normal functions of life. But the mouse has not been that informative to us and we are hoping that the cow will be more so."

The research is funded by the National Institutes of Health. The core objective of the NIH grant is to produce a cow that is genetically incapable of producing prions, and then determine whether or not the viability and function of the animal has been affected by the lack of the prion. Once the cow is cloned in late 2004, the researchers will conduct a number of behavioral and physiological evaluations of the animal.

If efforts to produce a normally functioning cow that lacks the genetic ability to code for the production of prions are successful, the researchers may have identified a strategy for finally containing the risks of this ominous disease.

While the prospects of "cloning" prion free cattle on the scale of America's 100 million head cattle herd may seen daunting, Eyestone points out that with the widespread use of artificial insemination in modern agriculture, great strides could be made in as little as six or seven generations.

On a smaller scale, sub-populations of prion-free cattle could be produced for use in other tasks such as the production of pharmaceutical compounds that are eventually used in people, thereby eliminating the risk that a drug produced to promote human health and well-being might accidentally cause the deadly neurological condition.