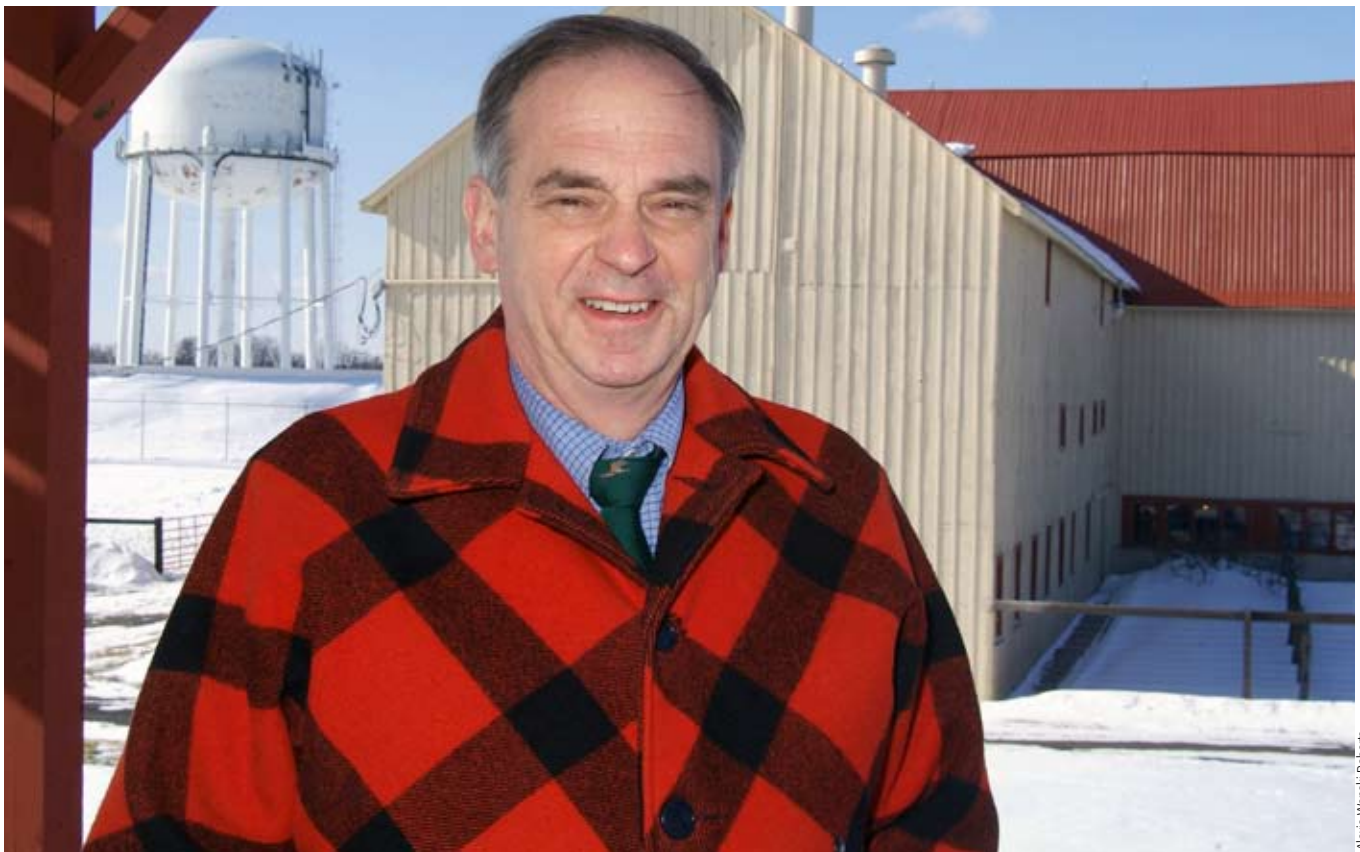


Zweig

Memorial Fund News Capsule

No. 43 June 2007

A report from the Harry M. Zweig Memorial Fund for Equine Research at the College of Veterinary Medicine at Cornell University



Alexis Wenski-Roberts

Douglas Antczak, who has spent nearly 30 years in the college conducting basic research, houses the horses, donkeys, hinnies, and mules that he breeds in the McConville Barn.

Studies in Equine Pregnancy Immunology Help Uncover the Equine Genome

When Professor Doug Antczak, VMD, PhD, talks about his life's work—researching equine pregnancy immunology with a detour into horse genomics—he credits the Harry M. Zweig Memorial Fund for giving him his first start.

A 1978 Zweig grant to a newly arrived Cornell assistant professor was the vote

of confidence that encouraged other funding agencies to support his work. Since then Antczak, who is the Dorothy Havemeyer McConville Professor of Equine Medicine and director of the Baker Institute for Animal Health, has become one of the world's leading experts on the genetics of immune responses in horses. ▶

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“That initial grant set in motion all that followed,” Antczak says. “Soon afterwards the Havemeyer Foundation initiated support for our program, and subsequently the National Institutes of Health (NIH) began to fund aspects of our research that are particularly relevant to human health.”

Support from these two organizations continues today, and thus the Zweig Fund has had a multiplier effect in attracting new external resources to Cornell’s equine research efforts.

Antczak’s research seeks to understand the mechanisms that prevent the mother’s immune system from rejecting the fetus that she carries during pregnancy. Mammalian pregnancy has been referred to as “nature’s transplant,” but unlike the situation in clinical organ transplantation, it is not necessary to identify a genetic match between mother and father, or sire and dam, to ensure success.

“We know that the immune system is responsible for graft rejection, and we also know the targets of this immune response—the proteins produced by the so-called histocompatibility genes,” Antczak explains. “What is not known, however, is how the fetus escapes detection and destruction by the mother’s immune system. Knowledge of these mechanisms should be important in understanding cases of pregnancy loss and, in addition, this research has relevance to organ transplantation in humans.”

The equine pregnancy immunology program requires expertise in reproductive biology, immunology, and genetics, and this is the link to the Horse Genome Project. For the past three decades, the Antczak laboratory has studied the genes and proteins of the

equine Major Histocompatibility Complex (MHC). The MHC proteins include the molecules that trigger the immune system to reject grafts and other molecules that help determine beneficial immune responses, for example, those mounted against viruses and bacteria.

“The horse genome sequence will fundamentally change the way equine research is conducted.”

Douglas Antczak

“Our studies of the equine MHC led us to a broader interest in horse genetics,” explains Antczak, “and here once again the Zweig Fund was instrumental in providing support for the early, cooperative efforts of the Horse Genome Project that began in 1995.”

The decade since then has brought incredible progress in horse genetics. Ten years ago only a handful of genes had been mapped in the horse. Today, the entire equine genome has been sequenced.

This has been accomplished through the work of equine geneticists from 22 laboratories in 12 countries who worked together to build a series of maps of the horse genome. This genetic framework led to the decision by the National Human Genome Research Institute to add the horse to the list of species for complete

genome sequencing. The multi-million dollar sequencing project was undertaken at MIT’s Broad Institute in Boston, one of the major U.S. sites for genome sequencing.

The whole genome sequencing project represents another way in which financial support from the Zweig Fund has been leveraged to provide new resources for the horse. The partnership between equine geneticists and the National Human Genome Research Institute will be beneficial to both parties. It is anticipated that the equine genome sequence will aid in the understanding of the human genome and, of course, there will be many applications to equine health.

“The horse genome sequence will fundamentally change the way equine research is conducted,” predicts Antczak. “It has already had profound effects in our own research. We can now obtain the sequence of virtually any horse gene from the online database. Just one year ago it could take a scientist up to three months to determine the sequence of a single gene, and now it can be done in 15 minutes.

“This really levels the playing field for the horse. We now have genomic resources comparable to those available for research on humans or mice. This is an incredible advance for equine research. In the coming year or two we expect to have access to commercial horse-specific microarrays that will allow us to study either genetic variation or gene expression across the entire equine genome. This will be revolutionary for horse research, and clinical application will likely follow very soon.” ■



McConville Barn



The McConville barn restoration received a Certificate of Merit from Historic Ithaca.

The eastern gateway to Cornell's campus on Route 366 is graced by a large, hand-hewn barn that has withstood the punishing Ithaca winters since the late 1800s. Originally known as the Mitchell Barn for the local family that had once farmed the land, the barn has served generations of Cornellians in many capacities. Home to Cornell's draft horses in the 1940s, the barn was also the site in the 1950s of Animal Science professor Robert Foote's pioneering studies of semen freezing that revolutionized dairy cattle breeding in this country and worldwide.

By the early 1980s, however, the barn had fallen into disrepair and was no longer used by the College of Agriculture and Life Sciences. Slated for demolition, new life was infused into the facility when Dorothy Havemeyer McConville, patron of equine research at Cornell, took an interest. Under the direction of Douglas Antczak, VMD, PhD, then a young assistant professor in the college, the barn was renovated and renamed after its benefactor. The restoration of the McConville Barn was highly successful and led to the award to the college of a Certificate of Merit from

Historic Ithaca.

Since that time, the barn has been home to the unique herd of horses, donkeys, mules, and hinnies that are used in a variety of equine research projects at Cornell, many of which are supported by the Zweig Fund. These projects include studies of the equine Major Histocompatibility Complex, equine allergies and immunodeficiencies, equine herpes virus infections, and the Horse Genome Project. Twilight, the DNA donor for the recently completed whole genome sequencing of the horse, was born at the barn and resides there today.

Over the years small improvements have continued to be made at the barn, increasing its utility as a resource for the college's equine programs. In September 2006 the Butler Family Pavilion, which sits on a knoll overlooking the Barn and its associated paddocks, was dedicated. The pavilion is used as an outdoor classroom for practical instruction and demonstrations involving live animals, and for informal lectures and presentations. Thus one of the Ithaca area's oldest surviving agricultural structures continues to find new uses in the 21st century.

Harry M. Zweig Memorial Fund for Equine Research 2007 Research Awards

New

\$47,560 to Dorothy Ainsworth for "Flavonoids Inhibit Inflammatory Mediator Production by Pulmonary Mononuclear Cells Exposed to Haydust"

\$24,897 to Norm Ducharme for "Steps Toward Novel Treatment of Laryngeal Hemiplegia: What Is Really Happening to the Airflow?"

\$45,000 to Tracy Stokol for "Defining the Cause of Thrombosis in Equine Inflammatory Disease: Role of Tissue Factor—A New Diagnostic Approach?"

\$36,838 to Gary Whittaker for "Emergency and Establishment of Influenza Virus in Equines"

Continuation

\$39,534 to Douglas Antczak for "Horse Genome Project: Functional Genomics through Equine Microarrays"

\$44,393 to Julia Flaminio for "How Does the Immune System of the Foal Fight Against *Rhodococcus equi* Infection?"

\$94,602 to Nikolaus Osterrieder for "Equine Herpesvirus Type 1 Virulence and Vaccine Efficacy"

\$39,672 to Bettina Wagner for "IgE and IgG(T) Antibodies in Allergy of the Horse"

Renewal

\$50,000 to Alan Nixon for "Joint Repair through Targeted RNA Interference and Anabolic Gene Induction"



Cornell's "Twilight" in the Limelight of the Horse Genome Project

When the first draft of the 2.7-billion-base-pair horse genome was placed in public databases this past February, a Cornell Thoroughbred had the distinction of being chosen as the horse whose genome was to be sequenced to represent *Equus caballus*, the domestic horse.

Twilight, a three-year-old mare, was selected because she is the most inbred horse in a special herd of research horses that Douglas Antczak, VMD, PhD, has raised over the past 25 years. Many of the horses in this herd have been selected for their Major Histocompatibility Complex (MHC) genes and are studied in Cornell's equine pregnancy immunology program. These horses have been instrumental over the years in many fundamental investigations of the equine immune system.

The Thoroughbred stallion Bravo, who is a close relative of Twilight, provided DNA for another important component of the Horse Genome Project, the Bacterial Artificial Chromosome (BAC) library. Large DNA clones from the BAC library form the backbone upon which the DNA sequence from Twilight is being assembled.

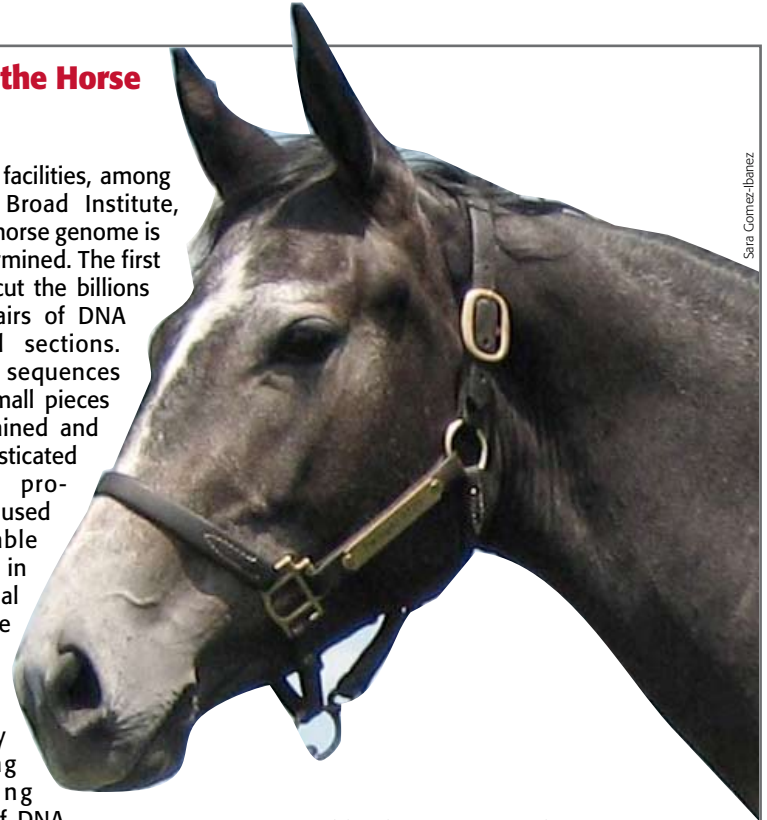
DNA sequencing technology has changed dramatically over the past decade and now much of the process is automated and carried out in large

centralized facilities, among them the Broad Institute, where the horse genome is being determined. The first step is to cut the billions of base pairs of DNA into small sections. The DNA sequences of these small pieces are determined and then sophisticated computer programs are used to assemble the pieces in their original order on the horse chromosomes.

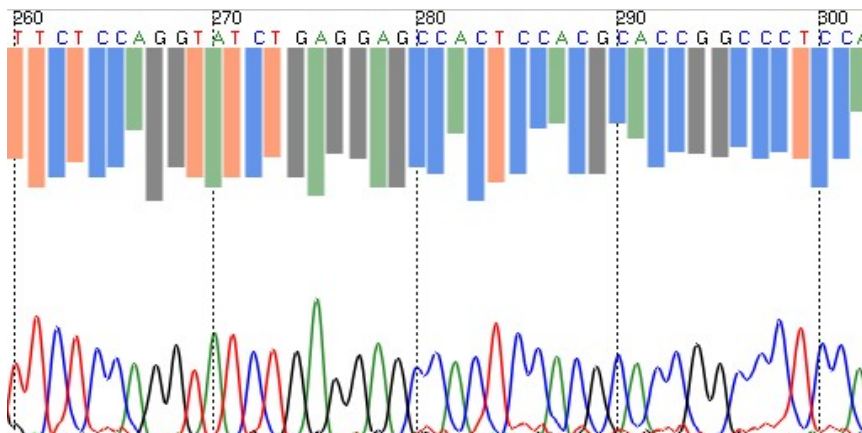
This is done by identifying overlapping stretches of DNA sequence that are shared by adjacent sections. This process is also aided by the framework of large clones of the BAC library created from the stallion Bravo. The assembly process is made easier if an animal has relatively little chromosomal variation, which is why Twilight was selected.

Sequencing the equine genome began in 2006 after a sample of Twilight's

blood was sent to the Broad Institute, a research facility run collaboratively by the Massachusetts Institute of Technology and Harvard University in Cambridge, Mass. Sequencing was completed in February 2007. The assembly is expected to be finished this summer.



Sara Gomez-Ibanez



A portion of DNA sequence from Twilight, the DNA donor for the whole genome sequence of the horse. This electropherogram was generated from one of the roughly 15 million clones characterized in the horse whole genome sequencing effort. This particular DNA segment is from a Major Histocompatibility Complex (MHC) Class I gene, an immunologically important gene that has been the foundation of Antczak's research for the past 30 years.

Don Miller—One Man Behind the Scenes

The year 2007 is a good time to research horse genomics. This spring the equine genome will be assembled from sequences completed last summer. That means it's a good time to work for Professor Douglas Antczak, VMD, PhD, an internationally renowned expert in the field.

So says research support specialist Don Miller, allowing that really any time is a good time to work for Antczak because the man is a wonderful boss.

"I really hit the jackpot," Miller says of Antczak, director of the Baker Institute for Animal Health. "Doug is thoughtful and considerate. He has created an excellent atmosphere in his laboratory that makes it a great place to work. He never objects to personal requests from his staff and I think that makes the individuals work harder to accomplish the lab's goals."

The admiration goes both ways. "Don has been a key member of the Horse Genome Project research team at Cornell for seven years," Antczak says. "He is an excellent researcher, and he also has a fine reputation as a mentor for the many undergraduates and veterinary students who have worked on this project over the past five years."

Recognition of Miller's expertise extends well beyond Cornell. In January of this year he was elected by the other members of the Horse Genome Project Workshop to serve as secretary (in 2008 and chair in 2009) of the annual Equine Program of the USDA's National Animal Genome Project. This program is held each January in conjunction with the Plant and Animal Genome Conference in San Diego.

"I'm honored to be asked to do this," Miller says, adding, "it is nice to be recognized by my colleagues."

Miller, who is the senior researcher in Antczak's lab, is co-author on two academic papers. He works alongside two veterinarians—one a PhD student and the other a postdoctoral fellow.

Miller, the son of a veterinarian, grew up on a horse farm in Cincinnatus, N.Y. After leaving college he began work as a groom for Standardbred trainer Billy



Alexis Wenski-Roberts

In addition to his contributions to research, Miller is a patient and thorough teacher of veterinary students who gain experience by working in the lab.

Haughton. He moved up through the ranks of Haughton's stable to the position of assistant trainer. "Working for the Haughtons was a great experience," Miller says. "I was surrounded by great people and horses."

After 15 years in the Standardbred industry, Miller married and moved back to central New York with his wife, Donna.

"Miller is an excellent researcher, and he also has a fine reputation as a mentor for the many undergraduates and veterinary students who have worked on the Horse Genome Project over the past five years."

Douglas Antczak

A daughter, Cassie, soon followed in 1997. "Cassie would live at the barn if we let her," Miller says. "She can't get enough of the horses."

In the fall of 1999, Miller was offered a position as a technician in the Antczak laboratory. He soon found that he had a natural talent for molecular biology

and became proficient in DNA and RNA isolation, PCR, and other molecular techniques. He assisted Zweig-funded researchers Julia Flaminio, DVM, MS, PhD, DACVIM, and Bettina Wagner, DVM, Dr. Med. Vet., by screening the newly available Equine BAC library for clones containing genes of interest. He continues to work collaboratively with Flaminio and Wagner, as well as with the scientists from around the world who are working on the Horse Genome Project.

"Doug's herd of horses and donkeys is a unique resource, and he is very generous in making reagents available to the horse community," Miller says. "We often get requests for samples from the herd or the BAC library and now many colleagues are interested in samples from Twilight due to her role in the whole genome sequence of the horse."

Miller also turned out to be a thorough and patient teacher; he eventually assumed responsibility for teaching the lab's summer veterinary students enrolled in Douglas McGregor's, MD, DPhil, Cornell Leadership Program for Veterinary Students and the Havemeyer Summer Fellows Program. Miller also assists the undergraduates in the lab, including some honors students. The names of some of these undergraduates appear alongside Miller's and Antczak's on posters from recent scientific conferences that hang on the wall outside the lab. ■

The Harry M. Zweig Memorial Fund for Equine Research honors the late Dr. Harry M. Zweig, a distinguished veterinarian, and his numerous contributions to the state's equine industry. In 1979, by amendment to the pari-mutuel revenue laws, the New York State legislature created the Harry M. Zweig Memorial Fund to promote equine research at the College of Veterinary Medicine, Cornell University. The Harry M. Zweig Committee is established for the purpose of administering the fund and is composed of individuals in specified state agencies and equine industry positions and others who represent equine breeders, owners, trainers, and veterinarians.



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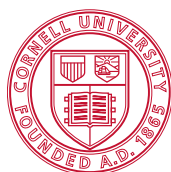
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