CEH HORSE REPORT

Volume 26 No 4, October 2008 A Publication of the Center for Equine Health, UC Davis School of Veterinary Medicine

Stem Cells and Regenerative Medicine in Horses

Every great advance in science has issued from a new audacity of imagination. ***— John Dewey (1859–1952)***

Regenerative medicine technology in humans and animals is advancing at a much faster pace than most of us realize. It has offered hope to thousands of humans suffering from diseases and injuries that destroy or damage vital cells. In animals, much of the research has been focused on orthopedic injuries in horses and dogs: bone fractures, arthritis and tendon and ligament injuries. There have been numerous clinical trials of stem cell therapy in these animals and the results have been quite encouraging. To this end, the Center for Equine Health has initiated a collaborative five-year research study to enhance our understanding of the behavior of stem cells for repairing bone, tendon and ligament injuries in horses. It is hoped that the knowledge and experience gained from treating horses in these areas will provide sufficient knowledge to not only establish scientifically verified treatment protocols but also support the translation of this technology into the human field.

What is Regenerative Medicine?

Regenerative medicine is the process of creating living, functional tissues to repair or replace tissue or organ function lost due to injury, disease, age or congenital defects. This field holds the promise of regenerating damaged tissues and organs in the body by stimulating previously irreparable organs to heal themselves: repair of damaged heart muscle after a heart attack, replacement of skin for burn victims, restoration of movement after spinal cord injury, regeneration of pancreatic tissue to produce insulin for people with diabetes, and so forth. Regenerative medicine can improve the quality of life by supporting and activating the body's natural healing.

What Are Stem Cells?

A stem cell is a "mother" cell that has the capacity for both replication and differentiation into other types of cells or tissues. Stem cells can

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DIRECTOR'S MESSAGE

A New Horizon in Equine Health Care

Dr. Gregory L. Ferraro

Regenerative medicine through the use of harvested stem cells is rapidly changing all of medicine. The stem cell and its ability to recreate, repair or revitalize damaged organs or tissues is rapidly bringing about fundamental change to the way medicine will be practiced in the future. It is bringing a factual new meaning to the adage that one should "heal thyself". Because now it is actually possible for medical scientists to use stem cells harvested from one's own body to fight disease and restore function. It marks a new dawn in medicine for humankind and all species of animals.

This bright new medical pathway is rapidly becoming an integral part of equine medicine as well. Scientists at UC Davis and elsewhere are developing new techniques and strategies for medical therapy almost on a monthly basis. The science of equine stem cell therapy is advancing so quickly that within 3 to 5 years, those treatments currently being provided for orthopedic repair in athletic horses will seem crude in hindsight. Additionally, it is evident to researchers that stem cells have the potential to make significant contributions to the treatment of many systemic medical diseases common to the horse—diseases such as laminitis, lymphangitis, neuromuscular degeneration and colic. Additionally, victims of burns and traumatic wounds should see improvements in both the quality and speed of their recoveries as a result of this new science. In fact, the possible benefits to the horse from the development of regenerative medicine seem to be an ever-expanding list. It is exciting and challenging work, and researchers at the UC Davis School of Veterinary Medicine combined with their partners from the UC Davis Stem Cell Program in the School of Medicine are right in the middle of it all!

Like all new areas of technology, stem cell therapy has the potential for misuse. The field of regenerative medicine is highly complicated and requires the involvement of skilled basic scientists to avoid ineffective therapeutics.

Like all new areas of science and technology, however, stem cell therapy has the potential for misuse. The field of regenerative medicine is highly complicated and requires the involvement of skilled and knowledgeable basic scientists and clinicians if ineffective therapeutics or outright abuses are to be avoided.

Thus, over the past two years the Center for Equine Health has developed a new *Stem Cell Regenerative Medicine Group.* This team of researchers combines the talent, skill and knowledge of 10 research and clinical faculty from 5 different academic departments within the School of Veterinary Medicine. The group, under the leadership of Dr. Larry Galuppo, also enlists the hard-working enthusiasm of 8 graduate students in the conduct of its research. Additionally, this group of veterinary scientists and equine specialists has established a working partnership with the UC Davis Stem Cell Program headed by Dr. Jan Nolta. Together, the knowledge and experience of all these scientists represent great leadership and optimism for the development of legitimate and effective regenerative medical techniques and stem cell therapies.

While there are many schools and institutions working in this new arena, as it stands now, the science of equine regenerative medicine has no better advocate, no larger talent pool, nor a more progressive research program than that assembled by the Center for Equine Health. In the pages that follow, we highlight the clinical applications that our research group is working to develop and outline some that are expected to arise in the near future. In the end you should come away with the same hope and enthusiasm for this new science as we have.

Stem Cells
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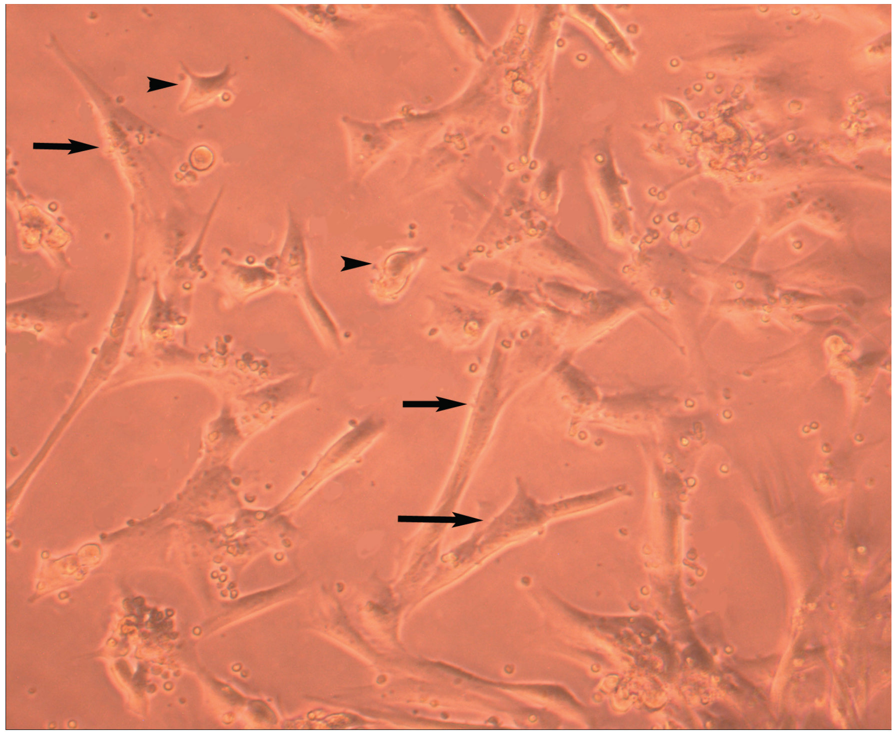
be induced to become other cell types of the body.

As most people are aware, stem cells can be derived from embryos. This source for stem cells has been controversial because of ethical considerations and the accompanying heated public debate. However, there are other valuable sources for stem cells that do not present ethical conflicts. These sources include umbilical cord blood and placental tissues collected during or after birth and adult stem cells derived from different parts of the body such as bone marrow, blood and fat.



Mesenchymal stem cells, shown by arrows, derived from umbilical cord blood. These cells will proliferate over time. Arrowheads point to round to triangular-shaped cells found in early culture that represent "contaminating" tissue cells. These cells will disappear with time.

Two types of stem cells are currently being evaluated for use in regenerative medicine: ***hematopoietic stem cells*** and ***mesenchymal stem cells***. Hematopoietic stem cells are typically found in bone marrow and can be induced to become various types of blood cells. Mesenchymal stem cells are found in the bone marrow, fat, umbilical cord blood and tissue, and many other organs throughout the body. Of the two types of stem cells, mesenchymal stem cells currently offer the greatest potential for regenerative medicine in animals, particularly in horses, because they can differentiate into many different tissues and cells including bone, cartilage, tendon and muscle.

Historical Perspective

The idea of transferring organs, cells and tissues from one location to another began centuries ago as a primitive practice and has since evolved into a modern reality. Medical scientists have been developing this capability for hundreds of years, allowing modern medicine to triumph over countless challenges along the way to achieve the success of today. Much more work is needed to continue the progress.

Regenerative medicine using stem cells has its origins in bone marrow transplantation, in which stem cells repopulate the marrow of the recipient and become both blood and immunologically active cells. The first successful bone marrow transplant was performed by Dr. E. Donnall Thomas in 1956. He subsequently published a report of his work to describe how fairly large amounts of specially prepared marrow could be given intravenously without ill effect to the patient. He envisioned potential applications of marrow transplants for treating not only bone marrow diseases such as leukemia, but also victims of radiation accidents—a chilling premonition of the 1986 Chernobyl Nuclear Power Plant accident in the former Soviet Union.

Thomas found that bone marrow grafts could be obtained with circulating blood as well as bone marrow and that the cells responsible for recovery could be frozen and kept for long periods of time. He continued to work on developing techniques for successful bone marrow transplantation, including pioneering techniques to prevent

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rejection of the transplant by the body's immune system.

By the 1970s, the number of long-term survivors and the number of diseases that could be treated in this way increased so that it was possible to use the term "cured" for these patients. Thomas was one of two physicians awarded the 1990 Nobel Prize in Physiology or Medicine for this work in cell transplantation in the treatment of human disease. Today, bone marrow transplantation has progressed from a highly experimental procedure to being accepted as the preferred form of treatment for a wide variety of human diseases.

What This Means for Horses

Although regenerative medicine technology using stem cells for tissue repair and regeneration is just in its infancy, several current uses are becoming more popular and gaining acceptance within the equine industry. These applications are in the treatment of bone fractures and soft tissue injuries. As laboratory and clinical research provides new knowledge, we will have a better understanding of the potential of these cells for use in many other clinical disorders.

At UC Davis, we have assembled a team of 10 research scientists to work together over the next five years to develop stem cells for clinical applications in horses. In its first year, the *Stem Cell Regenerative Medicine Group* has developed methods of cell collection from different sources and techniques for harvesting, culturing and long-term storage of these cells. Ongoing work is focused on determining how to administer and monitor cells for appropriate treatment applications in the repair of bone, tendon and ligament injuries.

Tendon and ligament injuries in performance horses are the most common disorders currently being treated with stem cells in clinical trials—specifically, tendonitis of the superficial digital flexor tendon or "bowed tendon." One researcher has shown a lower recurrence rate of bowed tendons in racehorses treated with stem cells (18%) compared with traditional therapies (56%). Other tendon injuries that are being treated with increasing frequency are lesions of the deep digital flexor tendon that occur in the pastern region and within the hoof capsule.

Clinical trials with local stem cell injection are also being performed for treatment of suspensory ligament injuries of the fore and hind limbs. Because there is a low success rate using various treatment methods for lesions of the origin of the suspensory ligament in hind limbs, more and more horses are being treated with stem cell therapy. We expect that several published studies will soon be available to describe the effectiveness of stem cell therapy for treatment of suspensory ligament disorders. Anecdotally, the results have been promising.

Degenerative joint disease is a problem in performance horses and has great economic impact on the equine industry. Although there are many therapies to support joint health, the majority of these treatments are to relieve the symptoms at best. Stem cell therapy for joint disease is supported by original research performed in goats. It was shown in an arthritis model of the stifle that joints treated with stem cells had less arthritic changes compared with nontreated joints in the same animal. Several horses have been experimentally treated for joint injuries at UC Davis using stem cell therapy and the initial results have been positive. It is likely that results from clinical trials will soon be available to document the effectiveness of stem cells for joint disease.

Fracture repair is an extremely challenging area of equine surgery. Many horses die of bone fractures due to the complexity of the injury and the inability to support the immense loads with current fixation equipment. Although bone grafts offer the advantage of containing live active cells that promote bone growth, there are several disadvantages. These include limited tissue availability, adverse effects on the patient's health caused when harvesting bone graft, potential graft rejection, and poor integration with native tissue.

One of the main challenges of bone repair in horses is the race between healing of the bone and either failure of implants (screws, plates) used for fixation or the

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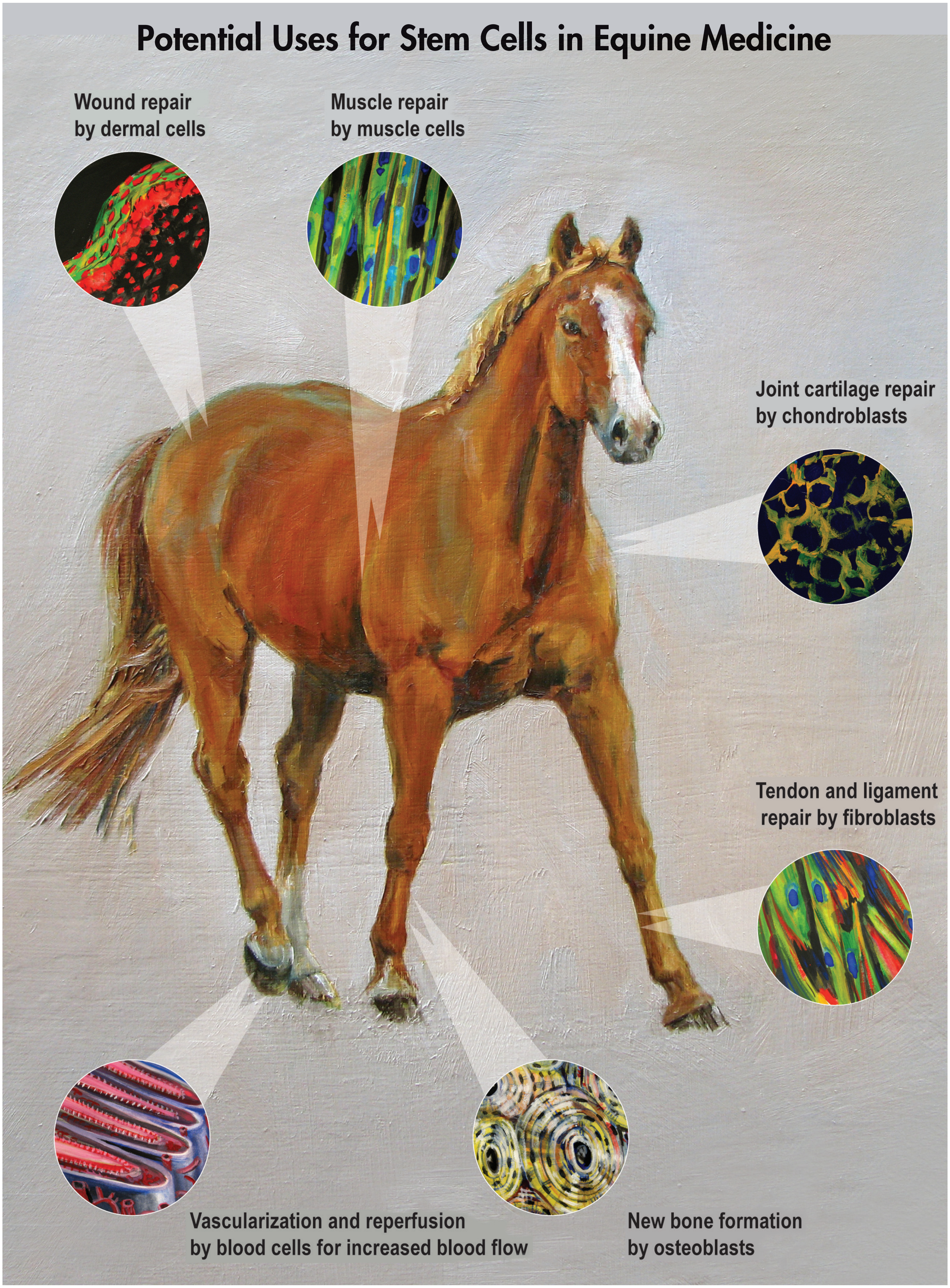
Potential Uses for Stem Cells in Equine Medicine
Wound repair
by dermal cells
Muscle repair
by muscle cells
Joint cartilage repair
by chondroblasts
Tendon and ligament
repair by fibroblasts
Vascularization and reperfusion
by blood cells for increased blood flow
New bone formation
by osteoblasts

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development of laminitis in the opposite limb. Because horses cannot remain lying down for long periods of time, the horse will spend a good deal of time standing on three legs if the fourth is fractured. Unfortunately, if a horse does not bear weight evenly on all four legs, the legs that are not injured can suffer terrible inflammation and changes in blood flow. The condition known as laminitis can become so severe that the horse cannot be sustained, as was the case with Barbaro and other famous racehorses.

Even with advances such as specialized bone plates being made in internal fixation methods, the repair of long bone fractures in horses is extremely challenging. One of the main areas where stem cell therapy may be valuable for fracture treatment is to speed bone healing. The potential of stem cells to provide such an improved treatment represents a major breakthrough in veterinary medicine. At this point, an intense research program focusing on use of stem cells for bone healing is underway at UC Davis. The information that will come from this five-year program will direct future treatment of fractures in horses.

This tibial fracture (left) in an adult horse was successfully repaired initially, only to fail (right) 5 weeks after the horse was standing comfortably in his stall. The horse had to be humanely destroyed after the implants failed before the bone could heal sufficiently enough to support the weight of the horse.

Laminitis is a common complication that occurs in horses during the period when the fracture is healing. Horses with repaired fractures will often bear excessive weight on the opposite limb, which results in detachment of the laminar connections between the hoof wall and coffin bone. Horses that develop extensive laminitis require humane destruction because of severe pain associated with this condition.

In addition to fracture repair, because of their robust bone-forming potential, stem cells may also be useful for regenerative therapies related to developmental bone disease. These conditions are commonly referred to as osteochondrosis (OCD) and have a tremendous economic impact on the equine industry. If a successful treatment for bone cysts could be developed using regenerative medicine technology, this would be one area where stem cells could produce a pronounced impact in both veterinary and human health. The UC Davis Stem Cell Regenerative Medicine Group is planning projects to investigate the use of stem cells for treating developmental bone disease during the upcoming year.

Research at UC Davis

Because mesenchymal stem cells currently offer the greatest potential for regenerative medicine in horses in their ability to differentiate into bone, cartilage, tendon and muscle cells, the UC Davis Stem Cell Regenerative Medicine Group has been working with these cells.

We recently developed a safe and easily accomplished method for collecting mesenchymal stem cells from umbilical cord blood and placental tissues during foaling. The process poses no threat to the health or safety of either the mare or foal. Once processed, these cells can be preserved by freezing and maintained for future use during the course of an individual animal's life. Current research also suggests that these placental-derived stem cells may have greater regenerative potential than cells derived from other tissue sources within the horse later in life. These cells may also be useful in treating disease among the parents and siblings within families of horses. These placental-derived stem cells represent an extremely valuable source of healing cell progenitors. Their collection and preservation at birth represent a sound strategy for maintaining future health and performance.

We have also found stem cells derived from bone marrow to be an excellent alternative source for therapeutic application. Bone marrow is easily extracted from the sternum of adult and juvenile horses. Recently, clinicians at the UC Davis School of Veterinary Medicine developed a new technique for harvesting bone-marrow-derived stem cells from the hip of horses under 4 years of age. This method is most suitable for yearling horses because it yields a large quantity of high-quality marrow in a safe and painless manner.

Fat from the body of horses and other animals (including humans) is also a ready source for stem cells. Fat tissue can be surgically excised at any time during life and manipulated within the laboratory to harvest stem cells for immediate use or for culture, expansion and storage for future use. These cells have been shown to have important therapeutic applicability and represent a valuable source of stem cells throughout the life of the patient.

Since stem cells are more potent in the younger animal, it would be beneficial to plan for the future and collect samples for stem cell culture and expansion early in the horse's life. For example, the collection and storage of bone marrow from horses under the age of 18 months is advantageous because it is well known and accepted by medical scientists that the quantity and quality of bone marrow-derived stem cells tend to decline with age. Therefore, if placental tissue stem cells have not been previously collected and stored, early collection and storage of bone marrow from valuable sport horse juveniles may prove to be a wise investment in the near future.

Banking cells is also recommended because it is likely that more than one treatment will be necessary for any given lesion as well as for future injuries that may occur while horses are actively training and competing.

There is still much to learn about stem cell therapy regarding treatment dose, timing, and frequency. It is difficult to derive a specific dose, but when treating various orthopedic disorders with pure populations of stem cells, anywhere between 5 and 10 million cells is currently being recommended. Based on research describing the anti-inflammatory effect and the ability of stem cells to orchestrate tissue repair and regeneration, early treatment should be beneficial. However, this will depend on the ability to bank stem cells and have a supply available immediately. Part of our research will be directed at development and refining methods to expand and store stem cells.

Because stem cells have the ability to target injuries and can help repair and regenerate damaged tissues, they may prove to be extremely valuable for treating many nonorthopedic disorders such as laminitis, exercise-induced pulmonary hemorrhage, left laryngeal hemiplegia, and neonatal maladjustment syndrome. As research advances in human medicine, disorders that are being evaluated for stem cell therapy in people will likely result in therapies for many equine diseases.

Being prepared for the future by banking stem cells will help veterinarians provide state-of-the-art therapies for many equine diseases.

Regenerative medicine technology is advancing at an extremely fast pace for many different disorders in humans and animals. Stem cell therapy in horses offers great promise for tissue repair and regeneration of tendon and ligament injuries, bone fractures, and joint disease. Being prepared for the future by banking stem cells will help veterinarians provide state-of-the-art therapies for many equine diseases. ❄

For a full version of this page, please click on separate link to ***Stem Cell Basics*** poster (printed size = 11" x 25").

Stem Cell Basics

Stem cells can be found in the different tissues of the body at all stages of life, before and after birth.
Stem cells differ from other kinds of cells in the body in that they generate progeny cells for organ formation and repair.
All stem cells, regardless of their source, have three general properties:

- **They are capable of renewing themselves for long periods through cell division (*proliferating*).**
- **They are unspecialized (*undifferentiated*).**
- **They can be induced to become specialized cell types such as muscle, blood and nerve cells (*pluripotent*).**

Stem cells come from different sources:

Embryonic Stem Cells

Human embryonic stem cells come from embryos that develop from eggs that have been fertilized in a test tube in an *in vitro* fertilization clinic and then donated for research purposes. They are not derived from eggs fertilized in a woman's body. The embryos are typically 4 or 5 days old and are a hollow microscopic ball of cells called the *blastocyst*.

Embryonic stem cells can produce any cell type found in the body.

Human embryonic stem cells have been controversial because of ethical issues surrounding the use of donated embryos. As a result, research was not supported by federal funding until recently.

On August 9th, 2001, President Bush announced that federal funds may be awarded for research using human embryonic stem cells if the following criteria are met:

- The derivation process (which begins with the destruction of the embryo) was initiated prior to 9:00 P.M. EDT on August 9, 2001.

- The stem cells must have been derived from an embryo that was created for reproductive purposes and was no longer needed.

- Informed consent must have been obtained for the donation of the embryo and that donation must not have involved financial inducements.

Research using human embryonic stem cells remains controversial in the United States and is still subject to intense political scrutiny.

Embryonic stem cells are not being actively investigated in equine medicine.

Umbilical Cord Blood Stem Cells

Umbilical cord blood stem cells are neonatal stem cells that can be obtained noninvasively and are abundant.

Cord blood is rich in ***hematopoietic stem cells***, which are most often used to treat human diseases.

Cord blood also contains ***mesenchymal stem cells***, which are being developed to treat bone, tendon and ligament injuries and diseases.

Today, human cord blood is collected and either banked or stored by private companies for future use in cell-based therapies.

In horses, veterinarians may attend foalings in order to collect blood from the cord and placenta for use in cell-based therapies.

Adult Stem Cells

Adult stem cells are actually found in the tissues of both children and adults. The term *adult stem cell* makes a distinction from *embryonic stem cell*.

Adult stem cells come from different parts of the body and have different properties, depending on where they are from.

The best characterized and most studied adult stem cells are the ***hematopoietic*** and ***mesenchymal stem cells***. Both stem cell types reside in the bone marrow and are easy to obtain.

The role of adult mesenchymal stem cells is to maintain and repair the tissues in which they are found. They can be thought of as the paramedics of the body.

Adult hematopoietic stem cells from bone marrow have been used in bone marrow transplants for 30 years.

Hematopoietic Stem Cells

Hematopoietic stem cells are adult stem cells found mainly in bone marrow and cord blood. They provide the blood cells required for daily blood turnover and for fighting infections.

Hematopoietic stem cells were the first stem cells to be used successfully in bone marrow transplants for leukemia and other blood disorders and have been used for decades.

It is still not known whether they can restore tissues and organs other than blood. Their potential to produce cell types other than blood cells is being investigated.

In horses, hematopoietic stem cells have not yet been isolated.

Mesenchymal Stem Cells

Mesenchymal stem cells are adult stem cells that are found in the bone marrow, blood, brain, fat and many other tissues.

Mesenchymal stem cells can be induced to form a variety of tissues, including:

- fat
- cartilage
- bone, tendon and ligaments
- muscle
- skin
- nerve

They can be obtained in large quantities appropriate for clinical applications.

Mesenchymal stem cells have been studied in great detail and scientists have advanced knowledge about how to grow these cells in culture.

Animal studies looking at the repair of damaged tissues such as cartilage, bone, muscle and tendon using mesenchymal stem cells have shown promise.

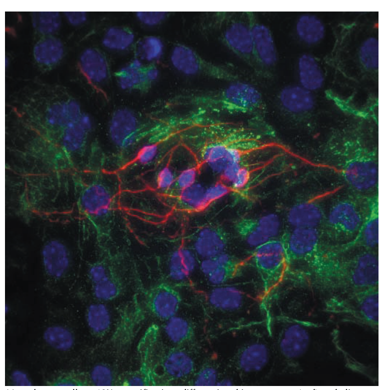
Mesenchymal Stem Cells and Horses

The therapeutic potential of mesenchymal stem cells in horses represents a major breakthrough in equine medicine, since fractures are often catastrophic and tendon and ligament injuries are a serious problem.

Currently, UC Davis research is focused on equine mesenchymal stem cells.

Mesenchymal stem cells can be isolated from a small sample of bone marrow, fat and umbilical cord blood and tissue.

All the equine stem cell sources showed capabilities to form bone in preliminary studies.



Neural stem cells at 40X magnification, differentiated into neurons (red) and glia (green). Glial cells provide support and protection for neurons and are thus known as the "glue" of the nervous system. Some undifferentiated neural stem cells are also present. Blue is a DNA stain. Image by Dr. Paul Kneopfler, UC Davis School of Medicine.

Definition of Some Common Terms

Proliferation = The process of cell replication many times over.

Differentiation = The process of stem cells producing specialized cells. Unspecialized stem cells are *undifferentiated* cells.

Plasticity = When stem cells from one tissue produce cell types of a completely different tissue, this phenomenon is known as *plasticity*. The same stem cell may produce both new blood cells and new muscle cells.

Pluripotent stem cells = The ability of stem cells to become all the cell types found in an embryo, fetus or developed organism.

Regenerative medicine = Medical interventions that aim to repair damaged organs, most often by using stem cells to replace cells and tissues damaged by injury, aging or disease.

Cell-based therapies = The most important application of stem cells is the generation of cells and tissues that could be used for treating diseases and injuries. Stem cells, directed to differentiate into specific cell types, offer the possibility of a renewable source of replacement cells and tissues to treat diseases such as heart disease and diabetes in humans and bone fractures and tendon and ligament injuries in horses.

Dick and Carolyn Randall, Core Sponsors of UC Davis Stem Cell Regenerative Medicine Group

Motivated by a desire to help broaden the exploration of regenerative medicine as a treatment option for companion animals and horses, Dick and Carolyn Randall of Cupertino provided core funding to launch a five-year, $2.5 million study of the therapeutic potential of adult stem cells.

Mr. Randall, a retired business executive and quarter horse breeder, has been riding reining horses competitively for more than 15 years. The Randalls' initial gift of $425,000 last December allowed the Center for Equine Health to organize and initiate the comprehensive regenerative medicine and stem cell research program in veterinary medicine.

The Stem Cell Regenerative Medicine Group includes 10 faculty members from five academic departments. It is housed at the Center for Equine Health and led by Dr. Larry Galuppo, Associate Professor and Chief of Equine Surgery in the School of Veterinary Medicine. The research team is collaborating with the UC Davis School of Medicine stem cell research program under the direction of Dr. Jan Nolta, one of the nation's leading stem cell researchers.

From left: Dick Randall, Dr. Gregory Ferraro and Dr. Larry Galuppo

Both the Center for Equine Health and the Center for Companion Animal Health are supporting graduate student researchers pursuing PhD degrees in conjunction with this project. The initial focus will be on using regenerative medicine for bone healing and repair in horses and dogs. Additional research will be performed in the application of mesenchymal stem cells for tendon and ligament injuries. Scientists will work to determine the most effective harvesting, propagation and long-term storage techniques for future banking of stem cells. They will also compare the bone-forming potential of mesenchymal stem cells derived from three different sources: fat, bone marrow and umbilical cord blood.

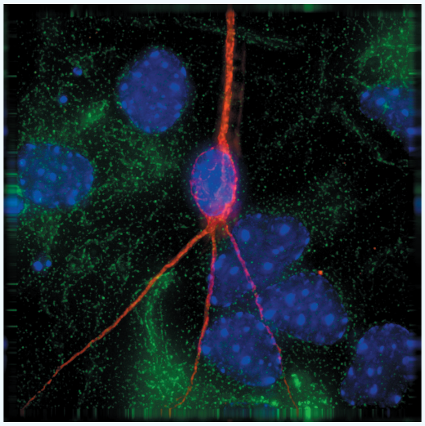
In addition to the support from Mr. and Mrs. Randall, funding has been received or pledged from:

- **The Harriet Pfleger Foundation**—for graduate student support.
- **Thermogenesis Corporation** of Rancho Cordova—for bioarchival equipment and graduate student and technical training
- **Alamo Pintado Equine Foundation**—for tendon ligament regenerative studies.

Volume 26, Number 4 - October 2008

Stem Cell Regenerative Medicine Group

UC Davis School of Veterinary Medicine



Neural stem cells at 100x magnification. Image by Dr. Paul Knoepfler, UC Davis

Our regenerative medicine team at UC Davis is comprised of faculty with diverse research interests that encompass musculoskeletal science, from its roots in the basic sciences to clinical investigation. The team has substantial overlapping research interests and operates in a highly collaborative atmosphere.

Dori Borjesson, DVM, PhD, Diplomate ACVP, Associate Professor, Department of Pathology, Microbiology and Immunology. Clinical expertise in comparative hematology and platelet and neutrophil function. Research focus on hematopoiesis and cell differentiation using bone marrow and cord blood-derived precursors; emphasis on mechanisms of cytopenias in tick-borne infectious diseases.

Larry Galuppo, DVM, Diplomate ACVS, Associate Professor and Chief of Equine Surgery, Department of Surgical and Radiological Sciences. Clinical expertise in orthopedic surgery with emphasis on fracture repair. Research focus on biomechanics of fracture generation, implant design and fracture biology.

Kei Hayashi, DVM, PhD, Diplomate ACVS, Assistant Professor, Department of Surgical and Radiological Sciences. Clinical expertise in orthopedic surgery with emphasis on fracture repair in dogs and cats. Research focus on orthopedic cell biology, cell-based tissue regeneration, joint pathology, fracture biology and comparative orthopedics.

Kent Leach, PhD, Assistant Professor, Department of Biomedical Engineering. Expertise in the synthesis and use of biomaterials derived from natural and synthetic materials, cell-to-cell interactions, controlled delivery of pharmacological molecules, and *in vivo* imaging. Research focus on the engineering and regeneration of replacement tissues.

Sean Owens, DVM, Diplomate, ACVP, Assistant Professor of Clinical (Diagnostic) Pathology, Department of Pathology, Microbiology and Immunology. Clinical expertise in transfusion medicine, cord blood collection and processing. Research focuses on red cell survival and red cell compatibility issues in horses following red cell transfusions.

Sarah Puchalski, DVM, Diplomate, ACVR, Assistant Professor, Department of Surgical and Radiological Sciences. Clinical expertise in cross-sectional imaging (CT and MRI) with an emphasis on equine lameness diagnosis. Research focus on the implementation of novel cross-sectional imaging techniques in equine orthopedics.

Susan Stover, DVM, PhD, Diplomate, ACVS, Professor, Anatomy, Physiology and Cell Biology, and Director, J. D. Wheat Veterinary Orthopedic Research Laboratory. Research focuses on etiopathogenesis and epidemiology of overuse, repetitive injuries in equine athletes; biomechanics of orthopedic injuries and fracture fixation; and musculoskeletal function in locomotion.

Fern Tablin, VMD, PhD, Professor, Anatomy, Physiology and Cell Biology. Blood and bone marrow physiology and cell biology, cryobiology and cellular preservation, stem cell biology, cellular and molecular platelet physiology.

Martin Vidal, DVM, PhD, Assistant Professor, Surgical and Radiological Sciences. Clinical expertise in orthopedic surgery with emphasis on treatment of tendon and ligament injury. Research focus on the use of stem cells and related therapeutics for regeneration and repair of tendon and ligament injuries in horses.

Clare Yellowley, PhD, Associate Professor, Anatomy, Physiology and Cell Biology. Orthopedic basic science research, musculoskeletal cell biology and physiology, stem cell biology, hypoxia, mechanotransduction, stem cells and fracture repair.

UC Davis School of Medicine's Stem Cell Program to Collaborate with Veterinary School's Regenerative Medicine Group

The Stem Cell Regenerative Medicine Group will be collaborating with scientists involved in stem cell research in the UC Davis School of Medicine — **UC Davis Stem Cell Program**, directed by Dr. Jan Nolta.


Dr. Jan Nolta

Dr. Nolta is widely recognized for her expertise in stem cells and is one of the nation's top stem cell researchers. Under her leadership, the UC Davis Stem Cell Program helps bring together resources from throughout the university to ensure that laboratory research can be translated successfully into clinical treatments for human patients.


Jan and her horse Zippy.

Dr. Nolta is also an avid horsewoman, having grown up in Northern California as a barrel racer. Although she doesn't have much time for riding these days, she relishes the opportunity to help horses by finding cures for diseases and injuries that adversely affect them.

UC Davis Stem Cell Regenerative Medicine Group Partners with Vantus of ThermoGenesis Corporation to Develop Stem Cell Technology

RANCHO CORDOVA, CA, FEBRUARY 27, 2008—ThermoGenesis Corp. (NASDAQ: KOOL), a leading supplier of innovative products and services that process and store adult stem cells, announced today that its wholly-owned subsidiary, Vantus, Inc., has signed a formal agreement with the UC Davis School of Veterinary Medicine's Center for Equine Health and its Stem Cell Regenerative Medicine Group. Under the agreement, the two organizations will conduct joint research and development of methods to enhance the collecting, processing and storing of stem cells from equine cord blood, bone marrow and placental tissue. These cells will be used in the development of therapeutics for the prevention and treatment of orthopedic injuries, such as tendon and ligament injuries, in performance horses.

Earlier this month, ThermoGenesis announced the creation of Vantus, a laboratory service company focused on the performance equine market, including Thoroughbreds, American Quarter Horses, Arabians and Warm Bloods. Under this collaboration, the ThermoGenesis MarrowXpressTM System and BioArchive® System will be used for processing and storage of the stem cells. The Company is currently refining collection methodologies at breeder farms in California and processing methods at UC Davis. Vantus expects to be in operation at the beginning of the foaling season in January of next year.

"As we have indicated, launching Vantus represents a major milestone in our regenerative medicine diversification strategy. By partnering with UC Davis, we are joining forces with a recognized world leader in veterinary medicine for the development of innovative therapies for treatment of injuries and disease in animals," noted Dr. William Osgood, Chief Executive Officer of ThermoGenesis.

"The risk of orthopedic injury to these high-value horses and their racing careers is well known. The potential for the use of stem cells to treat these debilitating, and often life-threatening, injuries is significant and we look forward to working with UC Davis on creating new forms of therapy for these horses," he added.

"The opportunities for stem-cell based therapies are significant and being proven every day. Leading veterinarians are now using stem cells in a variety of clinical conditions and the outcomes are very encouraging. We look forward to partnering with Vantus on the advancement of scientific discoveries and breakthroughs in this area," said Dr. Gregory Ferraro of the UC Davis Center for Equine Health.

Dr. Martin Vidal, New Faculty Member in the UC Davis School of Veterinary Medicine

Dr. Martin Vidal recently joined the UC Davis School of Veterinary Medicine as an Assistant Professor of Equine Surgery in the Department of Surgical and Radiological Sciences. He will also be joining the Center for Equine Health's research effort as a member of the *Stem Cell Regenerative Medicine Group*.

Dr. Martin Vidal

Dr. Vidal received his veterinary degree from the University of Liverpool in England in 2000. He was an intern in equine surgery at the Goulburn Valley Equine Hospital in Victoria, Australia, after which he returned to academia to pursue additional training. At Louisiana State University, he completed a residency in equine surgery and a Ph.D. in stem cell biology. He is board-certified by the American College of Veterinary Surgeons.

Dr. Vidal's primary research interests are in equine orthopedic diseases with a focus on the biology and application of equine somatic stem cells for regenerative tissue repair. His clinical commitment is divided into hospital service and equine surgery as well as teaching, with an emphasis on lameness evaluation and orthopedic diseases.

As a member of the *Stem Cell Regenerative Medicine Group*, Dr. Vidal will study specific biological properties of equine stem cells from varying tissue sources to determine methods of functional enhancement and optimization of stem cells for regenerative tissue repair. He hopes to shed light on the interactions between stem cells and natural tissue as well as stem cell mechanisms of healing tendons and ligaments.

The Horse Report Receives Recognition by American Horse Publications

For the fourth consecutive year, *The Horse Report* received awards from American Horse Publications (AHP) at the Annual Awards Program held June 21 in Saratoga Springs, NY.

Sixty-nine AHP members were named finalists in the 2008 AHP Annual Awards Contest for material published in 2007. A total of 105 AHP members and 1,092 entries participated in this year's contest. *The Horse Report* was awarded:

First Place in Service to the Reader (circulation under 10,000) for *Awakening the Dormant Dragon (Neurological Form of Equine Herpesvirus-1,* April 2007)

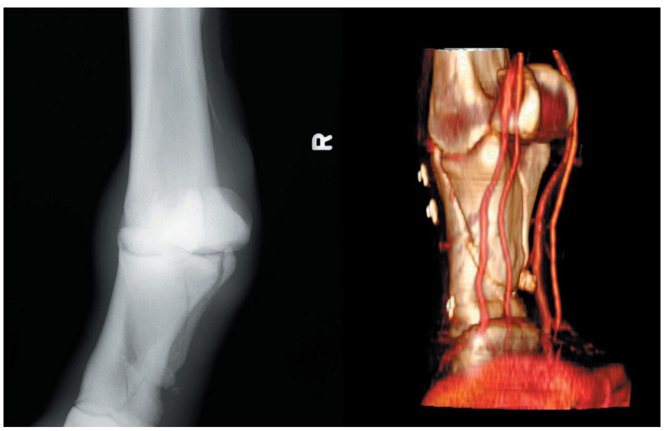
First Place in Equine-Related Newsletter (Print) for *Awakening the Dormant Dragon* (April 2007) and *Intestinal Parasites in Horses* (October 2007)

Third Place in Equine-Related Specialty Issue Publication for *Suspensory Ligament Injuries in Horses* (February 2007)

How Stem Cell Therapy May Have Helped Bailey Recover from a Bad Fracture

A Case Study from the Veterinary Medical Teaching Hospital

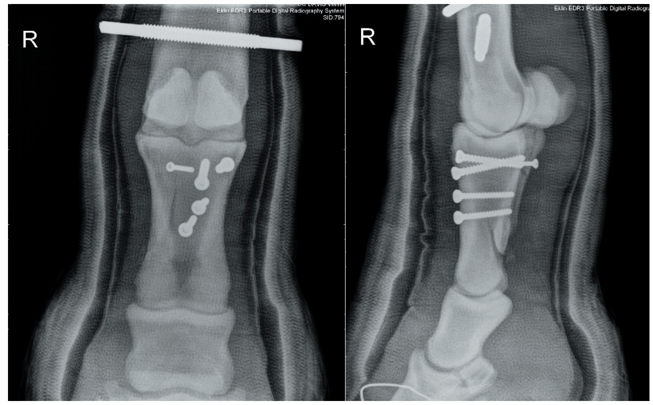
Bailey, a 12-year-old Quarter Horse mare, presented to the UC Davis Veterinary Medical Teaching Hospital with a severe fracture of her right front long pastern bone. Although the prognosis for saving her life was guarded, the owners elected to pursue treatment. A CT scan was performed to assess blood supply around the fracture and better understand the complexity of the injury.



***Left image**: An oblique X-ray of the right front limb showing a complete comminuted (broken or splintered into pieces) fracture of the long pastern bone, involving both the fetlock and pastern joints.*
***Right image**: A three-dimensional reconstruction of the CT scan with contrast material injected into the arterial supply of the lower limb. The imaging clearly shows the complexity of the fracture and documents that the main blood supply was still intact.*

The fracture was repaired with bone screws, and two bone pins were placed in the cannon bone above the fracture. The leg was placed in a cast to help protect the fixation during the healing period.

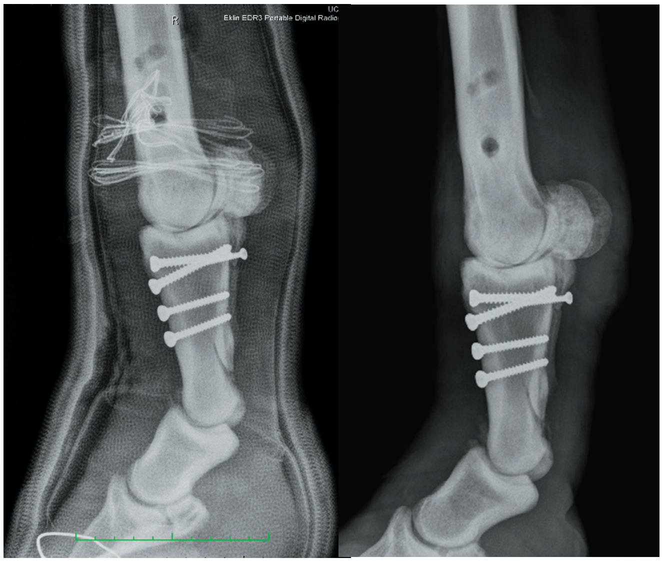
Bailey was recovered in a sling and placed in a hospital stall for postoperative care. Because of the severity of the fracture, a decision was made to use stem cells to enhance fracture healing. Bone



These are two X-rays showing the fixation with bone screws to reduce the fracture fragments and reconstruct the fetlock joint surface. Two threaded bone pins were placed in the cannon bone to protect the repair during the recovery period.

marrow was taken from the sternum and submitted to the UC Davis Regenerative Medicine Laboratory for expansion of stem cells. Bone marrow was harvested 12 days after surgery in preparation for local injection during the first cast change at 26 days post-surgery. At that time, stem cells were injected through needles placed through the skin into the fracture site at four locations. Radiographs were used to direct accurate placement of the stem cells. The leg was placed in another pin cast to protect the repair for an additional 4 to 8 weeks.

Bailey had several setbacks through the entire healing process. The main complication, which was not noted during the initial surgery, was severing of the ligaments from the sharp bone fragments on the back of the fracture. Loss of this ligament support caused her pastern joint to partially dislocate, resulting in instability and pain. The fracture showed evidence of being healed at 75 days, but the instability of the pastern joint was still a concern. Although it was likely that Bailey would need an additional surgical procedure to stabilize the pastern, she continued to improve clinically. After 102 days of hospitalization, Bailey was sent to a local lay-up facility for additional care. She was maintained in a bandage cast for an additional 45 days, at which time the cast was removed and a heavy bandage was placed to provide continued support.



***Left image**: A lateral X-ray showing that once the pins were removed the pastern joint partially dislocated. Tearing of the supporting ligaments by the sharp bone fragments when the fracture occurred caused this instability in the pastern joint, which complicated the overall recovery.*
***Right image**: A lateral X-ray showing healing of the long pastern bone fracture. However, there was persistent and progressive instability in the pastern, which could have required a second surgery to fuse the joint.*

Bailey continued to improve clinically, and one year after surgery she was bearing full weight without additional support on the limb and she was comfortable at the walk. The final radiographs showed fusion of the pastern joint and partial fusion of the fetlock joint, which allowed her to have a functional limb. Bailey did not show any evidence of laminitis during her entire recovery period. She has reached a level of stability and comfort to allow her to be used for breeding.

Although it cannot yet be scientifically proven that stem cell therapy substantially improved Bailey's chances for recovery, achieving these results without this additional therapy would be very difficult to accomplish. Further research is required to determine the ultimate effect of using stem cells for fracture healing, but this type of therapy is likely to be beneficial for enhancing healing in many types of fracture cases.

X-ray view of Bailey's fetlock one year after surgery. The pastern joint has fused with new bone production on the front and sides of the long and short pastern bones. The fetlock joint has also partially fused without a second surgery. Bailey was able to bear full weight without support and was comfortable at the walk.

Bailey during her recovery.

Upcoming Events

Californios Traditional Horsemanship & Pre-Roping Skills

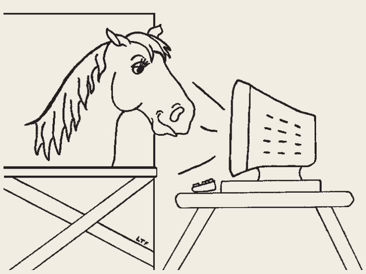
November 12–13, 2008
9:00 am–3:00 pm (no lunch break)
UC Davis Horse Barn

This two-day clinic focuses on good classical horsemanship and how it applies to practical working situations. Exercises are designed to further a horse's training while preparing for or doing a job. Some dry roping instruction included.

All ages and levels of ability welcome.
Tuition: $375 ($150 deposit)

For more information or to register contact **Dan Myers, (530)639-8806, dmmyers@ucdavis.edu**

VISIT OUR WEB SITE . . .



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The Center for Equine Health is supported with funds provided by the State of California Pari-Mutuel Fund and contributions by private donors.