



Gene Therapy

Conventional Arthritis Treatments

Trying to find an effective treatment for arthritis in horses can be a difficult, frustrating process for both horse owners and veterinarians. Conventional treatments are mainly anti-inflammatory. These medications reduce swelling, but do not protect the joint tissues against further damage. In an amazing advance in arthritis treatment, Dr. Dave Frisbie, a researcher with the Orthopaedic Research Center, has successfully used gene therapy to not only improve soundness in horses, but actually protect the joint tissues to prevent the arthritis from worsening.

Finding a Protein

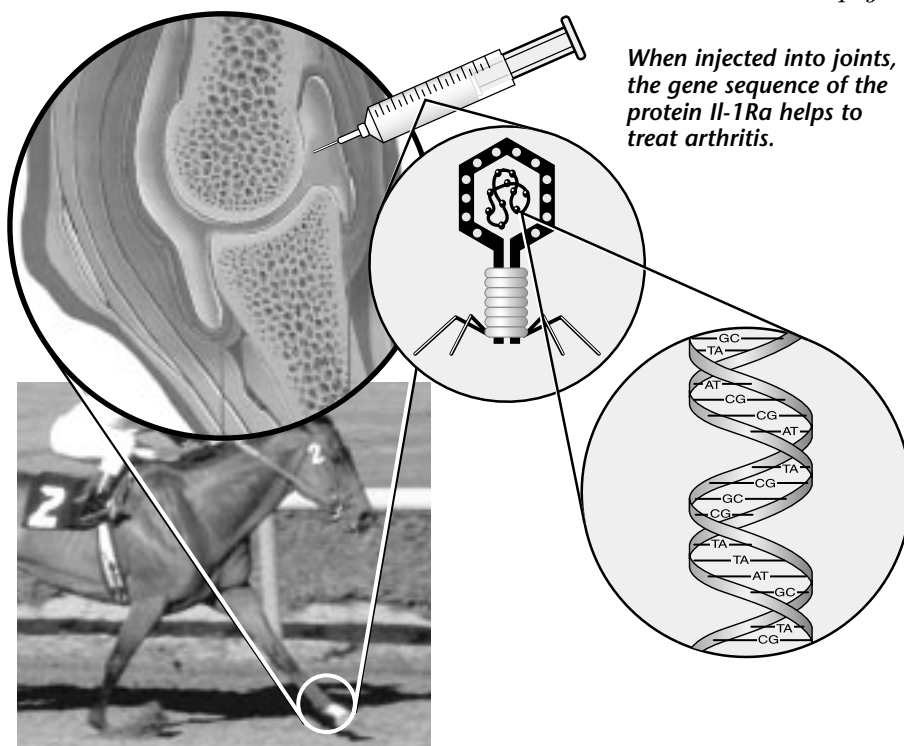
This success came after a long investigation, which began with the discovery that a protein called IL-1Ra was found in higher levels in people who had recovered from Lyme disease. One of the symptoms of Lyme disease is arthritis. This discovery led to the question: Could this protein ease the joint pain associated with arthritis?

Another protein, Interleukin 1 (IL-1), is an initial culprit in the debilitating progress of arthritis. IL-1Ra is the natural antagonist to the cartilage destroying protein, IL-1. The Orthopaedic Research

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Message from Dr. McIlwraith

As I hope you will find in this report, we have continued answering important orthopaedic questions for the horse and humans by successfully producing worthwhile research and gaining new research grant funding since the last issue. Our dedicated senior scientists, graduate students, and research associates continue to earn the confidence of granting agencies, corporate and private donors, manifest by receipt of excellent support for both ongoing and new projects within our focus areas of investigation.

Our continued growth and productivity and increased need for funding of personnel has created considerable pressure to complete our new research facility and to renovate the space allocated to us in the old Dairy Science building. These plans are progressing well. In the Year 2000, through a generous donation of \$600,000 from Herbert Allen and Gail Holmes, we acquired the \$1.1 million necessary to begin our new surgical animal care facility. The bad news is that since that estimate was made in 1998, we now require another \$500,000 and that is our current priority with fund raising. Additionally, with a \$250,000 donation by Barbara Cox Anthony, we achieved the \$900,000 necessary to complete renovations on the remainder of the Dairy Center, so it truly will become an Orthopaedic Research Center.

In addition to doing the research, we continue to disseminate the information at equine veterinary meetings and human orthopaedic meetings. In the past year we have been invited to present our cartilage healing research and the gene therapy work at a number of international human meetings. These speaking engagements are



consistent with our mission to help horses and humans. All faculty involved in the program also actively disseminate this important information at the horse owner level.

Fund raising remains a challenge. Our most immediate goal is to complete funding for the new center and then we will continue to pursue endowment funding so that we can offer long term security to our senior investigators. With a generous donation from the Dan Lufkin Foundation (through Elise Lufkin, a member of our Advisory Board), we have been able to hire a fund raiser specifically dedicated to the Orthopaedic Research Program to help fulfill our goals. We thank everyone for their past support and look forward to the future with enthusiasm.

Wayne McIlwraith
Director

Fundraiser Hired for Orthopaedic Program

A generous donation from the Lufkin Family Foundation has created a new fundraiser position, specifically for the Orthopaedic Research Center. Katie Ruggle began work as the new Associate Director of Development for the Orthopaedic Research Center in August.

Originally from Minnesota, Katie was previously involved in fundraising as the director of a humane society. She also worked as the manager of a dressage and jumping stable. Katie's undergraduate work was done in English and art, and she recently completed her MBA.



"This is a very exciting time for the Orthopaedic Research Center," she enthused. "I am thrilled to be a part of such a respected program. The scientists are accomplishing amazing things—especially in gene therapy and markers." Katie is also looking forward to working with other horse owners and trainers. "Horse people are great—very dedicated and giving."

Charismatic Fund

Charismatic's story began as a true Cinderella tale. The chestnut colt, despite being a grandson of Secretariat, had an uninspired start to his career. His owners, Bob and Beverly Lewis, and his trainer, Wayne Lukas, did not worry about losing him when they entered him in a \$62,500 claiming race in February 1999. They were delighted they did not, however, when, only three months later, Charismatic surprised everyone by winning the Kentucky Derby against 31-to-1 odds.

His Derby win was then followed by his Preakness win, which brought the colt only one victory away from the Triple Crown. The public's attention was caught. A record crowd of almost 86,000 people arrived at Belmont Park on June 5, 1999, to see Charismatic try for the \$5 million bonus that goes to a Triple Crown winner. As he was led into the paddock area before the race, the crowd gave a deafening roar.

Charismatic took the early lead, but, as two horses edged past him, tragedy struck.

"Heading for the finish," his jockey, Chris Antley, said, "he suddenly dipped underneath me, and I could tell he was in pain. He gave everything he had and ran as hard



Photo by Barbara Livingston

as he could, but he couldn't give the people what they wanted."

Charismatic came in third, just crossing the finish line before stumbling. Antley pulled him up immediately and leapt off, picking up the colt's left leg. The crowd, previously so enthusiastically loud, hushed in apprehension. Charismatic's leg had been fractured, shattering the dreams of his owners and trainer of a Triple Crown win. Fortunately, a two-and-a-half hour operation would save Charismatic's life. He would never race again.

With Charismatic now retired as a stud, his owners hope that he will pass some of his greatness on to his foals. Still, Bob and Beverly Lewis cannot help but wonder why this

tragedy happened and if anything could have prevented it. To find the answers and hopefully prevent the same injury from happening to another horse, the Lewises donated \$150,000 to create the Charismatic Fund to investigate equine condylar fractures.

CSU Equine Orthopaedic Center researcher, Dr. Chris Kawcak, is collaborating with Dr. Marcus Pandy of the University of Texas and Mike Torrey



Dr. Chris Kawcak

at the Steadman-Hawkins Sports Medicine Foundation to study the forces that are concentrated on the leg where the fractures occur. Computer modeling is used to understand how these forces can stress the bone. With a greater understanding of these forces, the researchers hope to be able to prevent some of the fractures like Charismatic's, and hopefully prevent other horses' careers, or lives, from being tragically cut short.



Dr. David Frisbie Receives Pfizer Award

Pfizer Animal Health awarded Dr. David Frisbie the prestigious Award for Research Excellence. This award honors "researchers whose innovative studies have advanced the scientific standing

of veterinary medicine" and is given to one young researcher at Colorado State University. Dr. Frisbie's impressive research achievements have made a significant impact in the field of orthopaedic health.

Orthopaedic Research Center: www.csuequineortho.com

“Magic” Markers

Predicting Future Musculoskeletal Diseases and Injuries

Predicting the Future

How many horse owners and trainers have uttered the phrase, "If only..?" If only they had known that early cartilage damage or a disease that could lead to a catastrophic fracture was present. Maybe, if they had known, they could have prevented the end of the horse's career, soundness, or even life. The ability to look into the future and predict a horse's impending orthopaedic injury or disease would be any horse owner's dream. Amazing as it sounds, researchers with the Orthopaedic Research Center are finding ways to allow horse owners to, in a way, predict the future. And sometimes, knowing the future means being able to change it.

The “Magic” of Markers

Markers are components found in body fluids such as blood, urine, and synovial fluid (the fluid surrounding the joints) that are early indicators of musculoskeletal disease and injuries. These components are the Orthopaedic Research scientists'

"crystal ball," enabling them to predict a horse's future health. Marker research has the potential to warn of impending fractures or future problems with OCD (Osteochondritis dissecans), a joint disease in young horses that results in fragmentation of the cartilage or bone.

The tools that are currently being used to diagnose musculoskeletal diseases and injuries, such as clinical assessment, radiographs (x-rays), ultrasounds, force plate gait analysis, and radioisotope bone scanning, make it difficult for veterinarians to diagnose the early changes that predict later injuries and disease. The current methods only allow diagnosis when significant damage has already been done. Because markers can potentially detect tissue changes in the initial stages, horse owners will have an early warning of possible problems before any serious damage is done.

A Bright Future

The researchers with the Orthopaedic Research Center, led



Dr. Clark Billinghamurst has led the marker research.

by Dr. Clark Billinghamurst, are making amazing advances in markers. They have proven that, using a panel of tests, chip fractures can be predicted with almost 80 percent accuracy. Current work is being done in many areas of markers, including a study headed by Dr. Billinghamurst and Dr. David Frisbie and funded by the Grayson Jockey Club Foundation, to find a marker that would predict, and therefore prevent, fractures. Dr. Billinghamurst and Dr. Frisbie are also working with Dr. Fahd Al-Sobayil, a Ph.D. student from Saudi Arabia, on a study which would separate changes in tissues which are only due to exercise as opposed to changes that are due to disease. Prince Ahmed Salman of the Thoroughbred Corp. is generously funding this study.

This exciting work in markers will continue at the Orthopaedic Research Center. It is hoped that, before too long, a simple blood test will predict future musculoskeletal injuries and disease in horses—preventing suffering in horses and heartbreak in horse owners.



A horse, Maude, is exercised on a treadmill by MJ Hamilton for a study separating markers caused by exercise from markers caused by joint disease.

Restoring Soundness Through Hoof Balance

The Foot of the Matter

As any farrier knows, a balanced, healthy hoof is the foundation of a sound horse. However, finding the best way to create that balance is not easy. Everyone has his or her own theory about the best method to trim hooves and the best shoes to use to retain soundness. Dr. Chris Kawcak and Dr. David Frisbie are trying to shed some light on this matter by conducting a two-part study comparing how well different shoes reduce the pain and lameness caused by hoof imbalance and navicular disease.

Nike for Horses?

The first part of the study compared three groups of horses: the first were unshod, the second had traditional steel shoes applied on all four hooves, and the third had a novel polyethylene shoe created by Dynamix in Switzerland applied. The researchers used a commercial thin film sensor to determine the pressure patterns in the hooves of the horses.

They discovered that the Dynamix shoe did help with the lameness caused by hoof imbalance. These findings led to a new question—would the Dynamix shoe also help reduce pain and lameness in horses suffering from navicular disease?

Navicular Relief

The second phase of the shoe study, currently underway, is comparing the effects of three different shoe types on horses with navicular disease. This is a clinical trial, which means that people who own horses with navicular disease are



The navicular bone [shaded] in relation to the other bones of a healthy foot.

encouraged to participate in the study.

Participants' horses have their old shoes removed, x-rays done, and video footage shot as the horses trot across a pressure sensitive mat. The mat measures the ground reaction force as the horse's hooves strike it. This allows the researchers to determine what problems the horses have.

The horse will then receive a trim and a randomly chosen shoe type,

either Egg Bar, Natural Balance, or Dynamix shoes, will be applied. The horse is then sent home with the owner with specific instructions for exercise and therapy. After four, ten, and sixteen weeks, the horse will be evaluated and reshod. For the last visit at the end of the sixteen-week period, the horse's owner can choose which type of shoes should be applied. The x-rays, trimming, shoes, and exams are all free to study participants.

The researchers are still looking for horses to be involved in the study. If you have a horse with navicular disease and wish to participate, please contact Helen Mawhiney at 970-491-4165.



Dynamix shoe is applied.



Left: Natural Balance shoe; Center: Egg Bar shoe; Right: Dynamix shoe

New Facilities Update

Excitement is building as plans for the new Orthopaedic Research Center are being finalized. This state-of-the-art facility will feature a surgical suite with an observation room, a visitor center, and offices, as well as 32 heated, deluxe horse stalls and several paddocks for the resident horses. The new building, combined with the newly renovated orthopaedic research laboratory, will allow the scientists to achieve a whole new level of research into preventing and treating orthopaedic problems.

Funding for the new Orthopaedic Research Center and remodeling of the laboratory was secured through private donations. A generous gift of \$600,000 from Herbert Allen and Gail Holmes brought the Building Fund to \$1.1 million, just \$500,000

short of the \$1.6 million needed to complete the new facility. Work on the laboratory renovation began in

August 2001, thanks in part to Barbara Cox Anthony, who donated \$250,000 toward the renovations.



COLORADO STATE UNIVERSITY
EQUINE ORTHOPAEDIC
RESEARCH LABORATORY
FORT COLLINS, COLORADO

Stallion Auction



"High Brow Cat", owned by Jack and Susan Waggoner of Waggoner Ranch.

Love is in the air...it must be almost time for the annual Cutting Stallion Auction benefiting the Orthopaedic Research Center and the Preservation of Equine Genetics Program. Each year in January, mare owners bid on breedings to the top cutting stallions in the country. This year, the auction includes high-quality stallions such as Docs Stylish Oak, High Brow Cat, Dual Pep, and Peptoboonsmal.

Thanks to Gail Holmes' tireless efforts organizing the auction each year and the generosity of the cutting horse community, this auction has been a wonderful fundraiser for equine orthopaedic and genetic research. Over the past four years, the auctions have raised almost \$250,000 for the two programs.

Updates and further details will be posted on the Orthopaedic Center's Web site (www.csuequineortho.com). If you have any questions about the upcoming auction, or wish to make a donation, please call or e-mail Katie Ruggle at (970) 491-3251 or kruggle@colostate.edu.



Photo by Gail Holmes

"Dual Rey" filly, owned by Holmes Cutting Horses.

Global Equine Research Alliance

What happens when four of the most respected equine orthopaedic research programs in the world merge their knowledge, resources and talents? The answer is good news for horses and horse owners. Researchers from four prestigious universities throughout the world: Colorado State University, United States; University of London, England; Massey University, New Zealand; and Utrecht University, the Netherlands, formed the Global Equine Research Alliance (GERA) in 1999. Their mission is to reduce the number of injuries occurring in equine athletes.

To Exercise or Not?

GERA's first major project is to study the effects of exercise on Thoroughbred foals' musculoskeletal systems. The information these studies will produce will be vital to horse owners who wish to raise foals to be healthy, sound athletes. It will also begin to answer the question of when is the best time to start young horses on a training program to ensure their long-term, musculo-skeletal health.

All the foals in the study, which is being done at Massey University, will be pastured and allowed to exercise at will. Half of the foals



Horse receiving a CT scan - one of several diagnostic techniques used to evaluate the early effects of exercise.

will also be on a training program with a gradually increasing level of exercise. The study will follow the foals until they are three years old and compare the differences in bone, cartilage, muscle, tendon, and ligament health between the two groups.

The researchers will use several different diagnostic techniques to evaluate the effects of early

exercise, including radiography (x-rays), ultrasound, computer tomography, and markers. GERA members will continue studies to further refine what exercise regimens are best suited for individual horses. The Marilyn M. Simpson Trust has had the generosity and foresight to fund Colorado State University's share of the GERA work.



Purdue Awards Dr. Wayne McIlwraith Honorary Doctor of Science Degree

Early 2001, Dr. Wayne McIlwraith returned from a trip to Australia to find that Purdue University was awarding him their most prestigious tribute: an honorary Doctor of Science Degree. On May 13, 2001, Dr. McIlwraith returned to Purdue, where he had received his master's degree and Ph.D., to personally accept the honor.

After he was presented with the degree, Dr. McIlwraith was given a book of letters supporting his nomination. Unbeknownst to him, over 40 of Dr. McIlwraith's peers and colleagues from around the world wrote to Purdue University in his support. The letters called Dr. McIlwraith "...the world's most pre-

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Congaree

The atmosphere was grim one early April morning in 1998 at Stonerside Stable, Bob and Janice McNair's Kentucky farm. Thoroughbred mare Mari's Sheba was struggling to foal, but, at 152 pounds, the foal was dangerously oversized. Attempts to help pull the tightly lodged foal from the mare only resulted in Mari's Sheba being dragged onto her side.

At two a.m., the chestnut colt was finally born—an hour and a half after his ordeal began. The grueling birth had broken two of his ribs and cracked three others. His lip was paralyzed and hung to one side, earning him the nickname, "Twitch." His first 45 days of life were spent in a stall, fighting for his life. Stable employees spent hours with the colt, trying to prevent him from puncturing his heart with one of his broken ribs. Because of his problems, and the time people spent with him, "Twitch" became a special pet. "Twitch," or Congaree, as he was later named, recovered from his birth injuries, only to be stricken



Photo by Anne M. Eberhardt

with pneumonia and diarrhea when he was only six months old. The farm manager, Bobby Spalding, did not think he would survive. The intensive nursing began again.

Amazingly, Congaree did recover, but his troubles were not over yet. He

made it to the Del Mar starting gate in September 2000, and placed sixth in a maiden race. After the race, however, x-rays revealed a bone chip in his right knee. Dr. Wayne McIlwraith from the Orthopaedic Research Center performed arthroscopic surgery to remove the chip. This resilient colt, who had been through more illness and injuries in his first two years than most horses face in their lifetimes, spent five months recovering from the surgery.

And recover he did! After three starts and three victories, including the Wood Memorial, Congaree was a prime contender for the 2001 Kentucky Derby. He finished third in the Derby and third in the Preakness

Stakes, delighting his owners and his trainer, Bob Baffert. He then went on to win the Swaps Stakes. Congaree is truly a success story—a homebred colt who fought for his life and soundness to emerge a great racehorse.

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Gene Therapy

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scientists isolated the DNA gene sequences that code for production of IL-1 and IL-1Ra, and this work, done by Dr. Rick Howard, led to current gene therapy research.

DNA Hitchhikers

Dr. Frisbie needed a way to get the IL-1Ra gene sequence into living equine cells. The solution, interestingly enough, was to use something that is not normally welcome by veterinarians—a virus. Viruses have evolved to be able to insert their own DNA into cells of

other organisms. This ability makes them a perfect vehicle for inserting foreign gene sequences into a horse's cells. Dr. Frisbie injected a harmless virus with the IL-1Ra's DNA into joints of horses with chip fractures. The virus inserted the IL-1Ra gene sequence into living cells, which made the cells adopt the DNA as their own. The cells then began producing the anti-arthritic protein.

Good News for Arthritic Horses!

Success! Compared to horses with similar bone chips but no gene therapy, the IL-1Ra horses became sounder, joint inflammation was

reduced, and, most impressive of all, the gene therapy actually halted the arthritis. The IL-1Ra stayed in the cells and produced the anti-arthritic protein for about 30 days before an immune response kicked them out.

More work is currently being done on gene therapy for the treatment of arthritis. This has exciting implications for both horses and humans suffering from joint problems.

The gene therapy research, which is supported by the Steadman-Hawkins Foundation, will hopefully help to heal cartilage defects and further alleviate the suffering of many who are living with arthritis.

Reactive Oxygen in Diseased Joints

Sharing Information— From Humans to Horses

Much of the work on horses done at the Orthopaedic Research Center is tied in very closely to studies involving human orthopaedic work. The more that equine and human researchers discover and share with each other, the larger the arsenal of weapons to fight orthopaedic injuries and diseases becomes—a win-win situation for the scientists, people and horses.

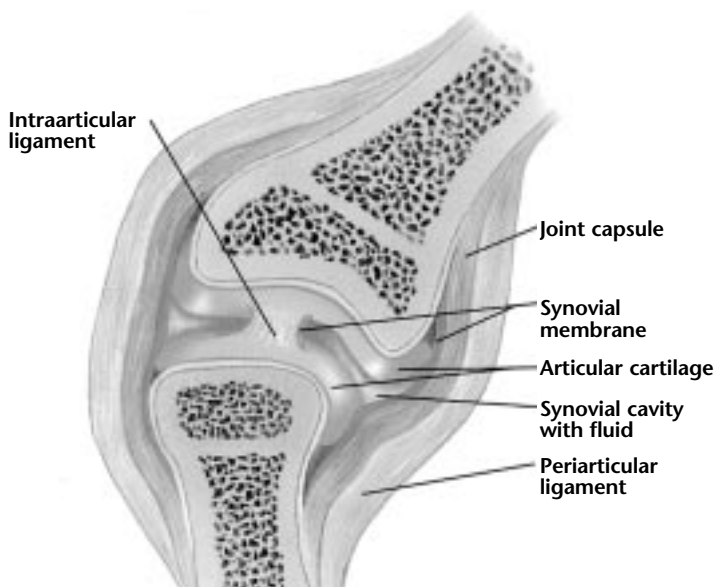
One study, headed by Dr. Paul Siciliano and involving graduate student Abigail Dimock, investigated Reactive Oxygen Species (ROS), also known as Free Radicals, a type of molecule that degrades joint components. ROS have also been found to worsen joint disease in humans. Dr. Siciliano was attempting to discover if this culprit of joint disease in the human athlete is also a contributor to similar problems in the equine athlete.

Reactive Oxygen

To discover if ROS did contribute to joint problems in horses, Dr. Siciliano took samples of

synovial fluid (the fluid around the joint) from both normal horses and horses undergoing arthroscopic surgery with Dr. Wayne McIlwraith. Both Quarter Horses and Thoroughbreds were used in this study. The synovial fluid was tested for the level of protein carbonyl content, which is a marker (see more about markers on page 4) for damage done from ROS.

Dr. Siciliano and Dimock did find that the levels of protein carbonyl content were significantly higher in diseased joints than in healthy joints. This research could open the door to therapy dealing directly with the reactive oxygen species. Free radical scavengers are currently used to reduce the number of ROS in humans. One example of free radical scavengers is Vitamin E, which is found in most green vegetables. This human/horse crossover research is just one way that the scientists at the Orthopaedic Research Center are working to increase the ways to heal joint tissue and halt the progress of joint disease.



On-Line Giving

Making a contribution to the Orthopaedic Research Center will soon be easier than ever—just point and click! This fall, visitors to the Center's Web page will be able to make a donation by filling out a short form on-line. This secure giving form will be easily accessed from the Orthopaedic Web page menu. Supporters of the program will be able to quickly and safely give electronically to either the Building Fund or Endowments for the Orthopaedic Research Center.

Visit the Orthopaedic Research Center's Web page at:

www.csuequineortho.com

Purdue Award

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eminent equine surgeon..." and "...the premiere researcher in the veterinary profession." His achievements "...have set new heights and expectations for every field in veterinary medicine." His colleagues also praised him personally, calling him, "brilliant," "committed," "a true leader," and "remarkable." The letters glowed with admiration, unanimously and enthusiastically recommending that Dr. McIlwraith be awarded the Doctor of Science Degree.

That many top veterinarians cannot be wrong! The accomplishments of Dr. McIlwraith and the Orthopaedic Research Center truly are amazing—not only for the individual surgeries that have saved horses' lives and returned them to successful careers, but also for the ongoing research which is continually improving joint health for horses and humans.

Orthopaedic Research Center Supporters

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Green Level – \$100 to \$999

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Von Hemel Racing Stable (NE)
James A. & Juanita B. Winn (AZ)
Wisconsin Equine Clinic (WI)
Patrick H. Young (OK)



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Orthopaedic Research Center

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Arthros is an annual CSU Orthopaedic Research Center publication.

Our Purpose:

To find solutions to musculoskeletal problems, especially joint injuries and arthritis in horses and humans.

Our Philosophy:

To offer the best treatment of clinical cases possible, with continued and critical assessment of our results; to use these results to change our treatments; to point our research toward prevention of problems we cannot treat effectively or that cause permanent clinical damage.

Our Goals:

To find new methods to heal joints already damaged; to use state of the art research techniques to find ways to prevent the occurrence of joint diseases and musculoskeletal injuries; to find methods of early treatment to prevent permanent damage when joint disease does occur.

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Opportunities for Private Giving

It is an exciting time for the Orthopaedic Research Center!

The lab is currently under renovation, groundbreaking on the new orthopaedic facility is imminent, and the scientists are making enormous strides in advancing the treatment and prevention of orthopaedic problems. The support of the individuals, foundations, and corporations who recognize the quality of the program and understand the importance of the Center's research made all of this possible.

To all those who have donated to the Orthopaedic Research Center—thank you. Your support is invaluable. Hopefully, you will continue to make it possible for the researchers to improve the health and quality of life for both humans and horses.

There are a variety of ways for an individual or group to make a tax-deductible charitable contribution.

Outright Gifts

Cash: Cash, usually given in the form of a check made payable to the Colorado State University Foundation, is available for the Orthopaedic Research Center to use according to your wishes.

Securities: Stock certificates are delivered either directly to the

Foundation with endorsed stock powers or through an intermediary such as a bank or broker.

Gifts-in-Kind: Whole or partial interest in valuable items such as art, antiques, computers, laboratory equipment, horses, coin collections, or jewelry can be donated.

On-line Gifts: Credit card gifts can be made on-line through a secure, confidential form accessible from the Web page.

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Bequest: A specific percentage of the full estate, or the entire estate, is left to the Colorado State University Foundation in your will.

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control of the funds, but still retain a life income from the funds. After you and any other beneficiaries die, the remainder of the funds comes to the foundation. These trusts may take effect while you are alive or may be created by your will.

Charitable Lead Trust: A gift of a specified amount is placed in a trust for a specific period. During that time, the Foundation receives the income from the trust. When the period of the trust ends, the principal is returned to you or a beneficiary. Typically, you are not taxed on the income received by the foundation during the life of the trust.

Real Estate

A gift of real estate may be made as either an outright gift or a planned gift.

There are many ways to help the Orthopaedic Research Center. If you have any questions about making a gift or wish to discuss financial matters concerning your contribution, please contact Paul Maffey, Director of Development, College of Veterinary Medicine and Biomedical Sciences, at (970) 491-3932 or e-mail r.paul.maffey@cvmbms.colostate.edu.

Thank you.



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Contact Paul Maffey, College of Veterinary Medicine and Biomedical Sciences, if you have any questions or need additional information.
Phone (970) 491-3932.