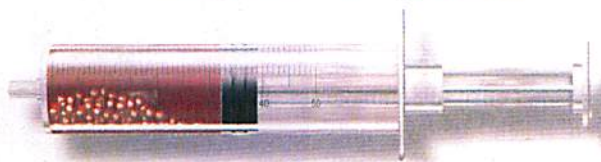


HORIZONS IN HEALING

Some horses who do not respond to conventional treatments for joint and soft tissue inflammation are now making astonishing progress with this recent therapeutic option.



By Laurie Bonner

At some point in their careers, most horses experience some degree of soft tissue injury, joint inflammation or osteoarthritis. Whether it results from the aftermath of an old injury or the accumulation of decades of wear and tear, the stiffness, lameness and swelling in one or more joints is common, and in some, the pain can cut short a promising career.

A number of medications are available to ease the pain and reduce inflammation, and treatments include joint injections with corticosteroids or biological agents such as hyaluronic acid (HA) or PSGAGs[®]. All have their benefits, but some have side effects, and then there are the horses who simply don't respond well to any of them. In those cases, there's little to do besides scaling back a horse's activities and preparing to retire him.

In 2004, however, a new treatment was introduced in the United States

that offers hope even for difficult cases of joint or soft tissue injury. Therapy based on IL-1ra (interleukin-1 receptor antagonist protein) employs a horse's own blood to reduce inflammation and promote healing.

"The prime advantages are that IRAP uses 100 percent of the body's own medicine," says Julio Reinecke, DVM, PhD, co-inventor of the IRAP therapy method and managing director of Orthogen AG in Düsseldorf, Germany. "It's sterile, and it can be used repetitively."

IRAP therapy is now widely available, and it is often used to treat arthritis as well as other inflammatory injuries of tendons and soft tissues around joints. And in many cases, it has restored soundness to horses previously thought to be hopeless. "IRAP is like other medical treatments; it does not work in every case but does help some horses that cannot be helped using conventional methods," says David Frisbie, DVM, PhD, of Colorado State University.

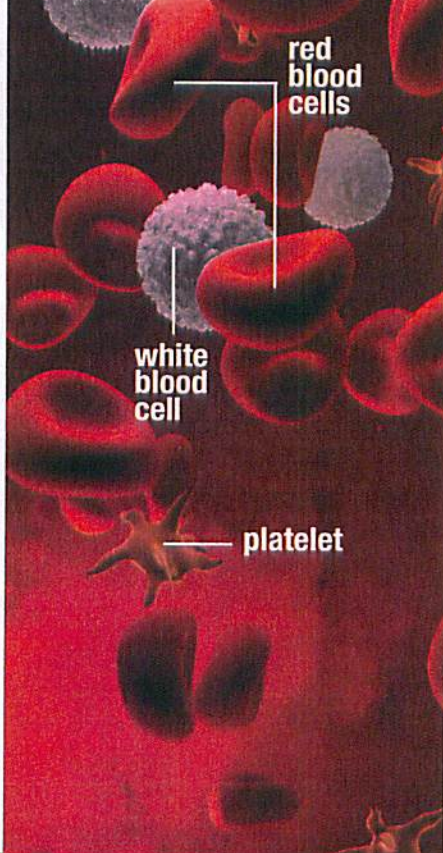
Here's a closer look at how IRAP therapy works and how it can help horses.

BRINGING BALANCE TO THE HEALING PROCESS

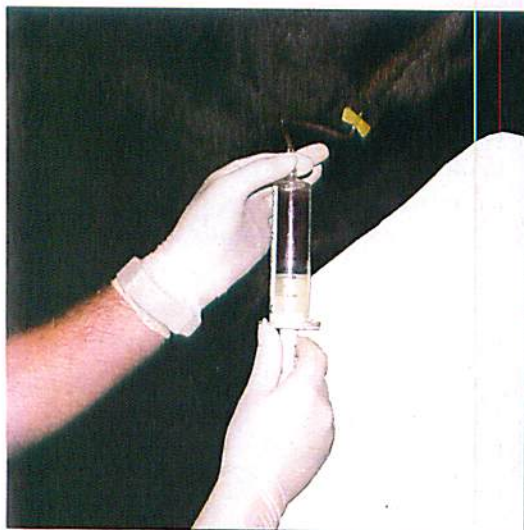
IL-1ra is a cytokine, a protein that attaches to and produces an action on a living cell. When used therapeutically, IL-1ra blocks the action of another type of cytokine, interleukin-1, that promotes inflammation.

Inflammatory processes are essential to the repair of injured tissue. And, under normal circumstances, the body's pro-inflammatory forces are kept in check by natural anti-inflammatory cytokines, which help restore the tissue environment to normal once the damage has been repaired. When cells wear out or are damaged, they must be destroyed to make way for replacement cells. Damaged cells release biochemicals that lead to the production of interleukin-1, which attaches itself to receptors on cell membranes and stimulates the production of enzymes (especially matrix metalloproteinases, MMPs), which in turn break down collagen

THE IRAP PROCESS



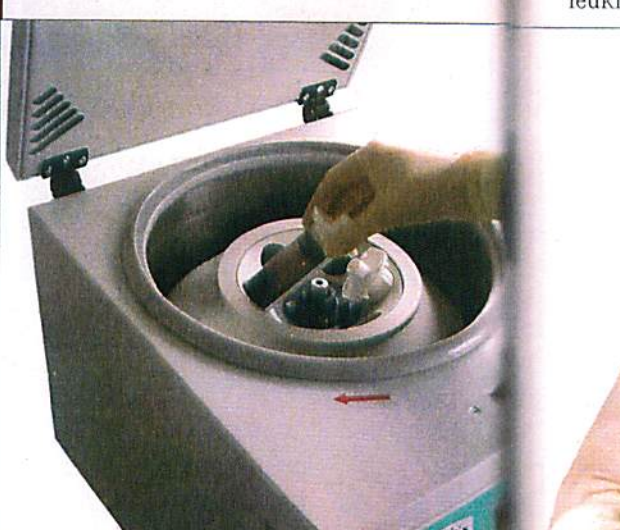
The syringe used to draw blood for IRAP therapy contains glass beads that have been specially treated to increase the surface area that comes in contact with it. "White blood cells recognize the surface of the glass spheres as 'foreign,'" says Julio Reinecke, DVM, PhD, co-inventor of the IRAP therapy method and managing director of Orthogen AG in Düsseldorf, Germany. The white cells adhere to the textured surfaces, which stimulates them to produce anti-inflammatory and regenerative proteins. "One of these is interleukin-1 receptor antagonist [IL-1ra] in addition to other cytokines and growth factors."



STEP ONE: A veterinarian draws about 50 milliliters of the horse's blood into an IRAP syringe.



STEP TWO: The blood sample is incubated in the syringe for about 24 hours.



STEP THREE: After incubation, the syringe is spun in a centrifuge to isolate the serum, the clear yellowish fluid minus the red cells and other solid components.

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S and aggrecan, the solid components that give cartilage its structure and strength. This activity paves the way for new cells to grow in.

However, if an injury is extensive, or the rate of cell destruction outpaces the body's healing processes, the pro-inflammatory cytokines may proliferate unabated, outnumbering and overwhelming the anti-inflammatory forces. When this happens in a joint, the flood of destructive enzymes breaks down cartilage as well as the synovial fluid. This increases wear on the bone ends, which in turn stimulates more inflammation—a vicious cycle that can continue until much of the protective cartilage within the joint is destroyed. This out-of-control inflammatory cascade leads to an advanced case of osteoarthritis, which can cause permanent and debilitating lameness.

IRAP therapy works by halting this cycle or preventing it altogether. IL-1ra has the same molecular “keys” as interleukin-1, and it binds to the same receptor sites on cell walls that interleukin-1 would normally occupy. When

interleukin-1 is prevented from binding to those sites, it cannot stimulate the release of the destructive enzymes that break down cartilage. “By using IRAP as a treatment we provide the protein or anti-inflammatory agent at a much higher concentration than it would be found naturally and at the site where it is needed most,” says Frisbie.

FROM LAB TO REAL LIFE

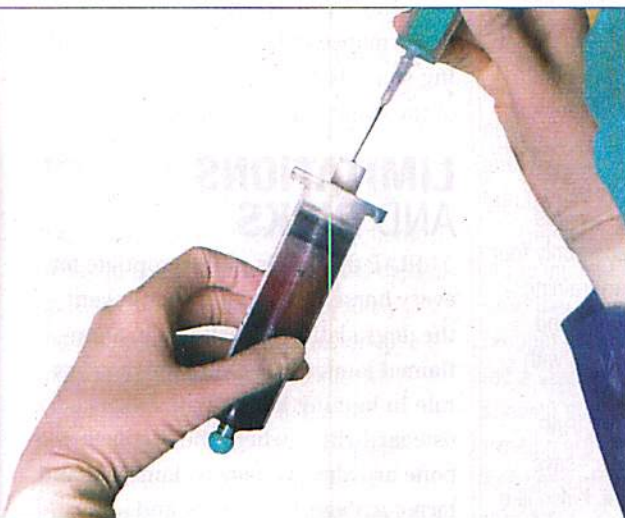
IRAP therapy has been shown to improve soundness in arthritic horses who had not responded to other forms of therapy, and it has proven to be safe, with little risk of adverse reactions. In a 2007 study at Colorado State University, 16 horses with a similar degree of osteoarthritis were used to study the effectiveness of this treatment. Eight were treated with IRAP therapy; eight received placebo treatments. After the study period, the horses who received IRAP were significantly less lame than the control or placebo-treated horses, and the joint tissues and the synovial

fluid—the viscous lubricating fluid within the joints—looked significantly healthier in the IRAP-treated horses.

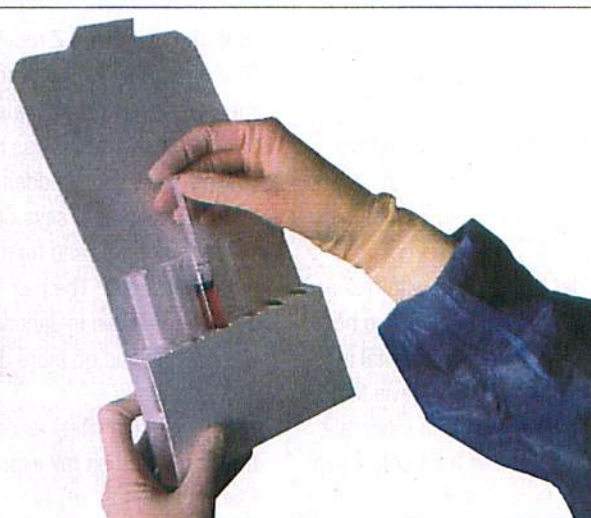
“We believe that for a number of indications the IRAP treatment is very well suited,” says Reinecke. “It combines ‘anti-inflammation’ very efficiently without many of the side effects that normal drugs may have. Joints and soft tissue respond well in cases of acute or chronic disease with an inflammatory manifestation. Veterinarians have also used [IRAP treatment] in cases of kissing spine or nerve root irritations.”

No other peer-reviewed studies quantifying success rates of IRAP therapy in horses have yet been published, but a retrospective study is under way. Reinecke estimates that to date close to 70,000 horses all over the world have received IRAP therapy, with generally good outcomes.

IRAP therapy is becoming increasingly popular throughout the United States, especially at sports-medicine practices. Before IRAP therapy was an option, says Carrie Schlachter, VMD, of



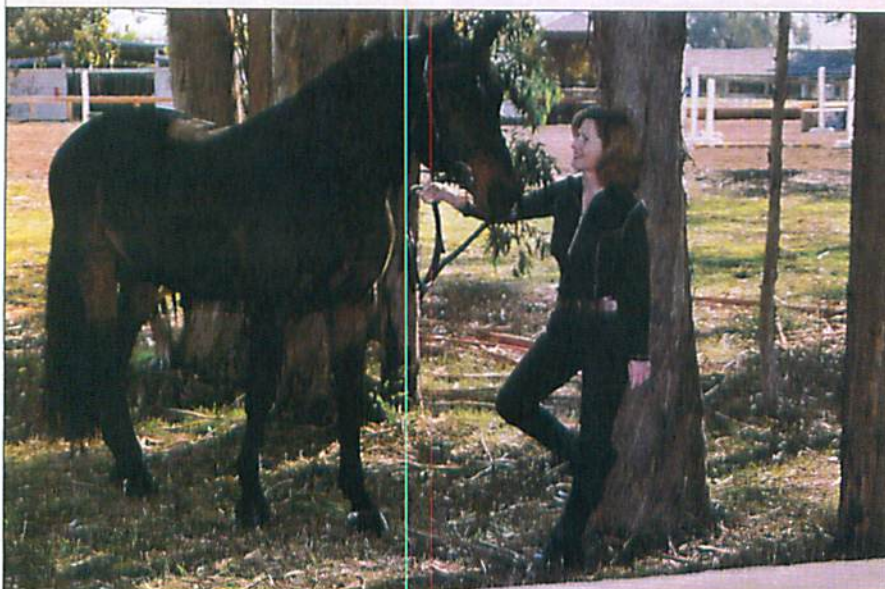
STEP FOUR: The result, called autologous conditioned serum (ACS) because it contains high levels of anti-inflammatory proteins, is then divided into four to six doses.



TREATMENT BEGINS: The IRAP doses are administered at one- to two-week intervals.



CASE STUDY: "PLAN B" SUCCEEDS



Dario Z was lame but steroid^o treatments, clearly, were not an option. Just hours after the 7-year-old Belgian Warmblood received a corticosteroid injection in his left front coffin joint, the area "flared" with pain and swelling.

"I was told that a small percentage of horses will flare and that you simply cannot use steroids for them," says Clara, Dario Z's owner. The young horse had come up lame in June 2009.

"I was away most of May, and we also changed shoers that month," Clara explains. "When I returned in June he was not quite right."

Dario Z did not improve with rest and anti-inflammatory medications, so he was sent to the veterinary hospital at the University of California–Davis for an MRI^o, which revealed mild to moderate inflammation in the left front coffin^o joint and moderate to severe inflammation in the bursa^o sac.

But when the standard treatment—an injection of corticosteroids into the joint—produced the flare, the horse had to be

BACK ON TRACK: Warmblood show jumper Dario Z returned to soundness after undergoing IRAP therapy for inflammation of the coffin joint.

kept at the hospital for an extra night.

Plan B, as recommended by Dario Z's veterinarian Carrie Schlachter, VMD, was IRAP therapy. Dario Z received his first IRAP treatment in September 2009, and the injections were repeated over the next few months while he was rested and hand-walked, then gently ridden.

"By December," says Clara, "he was 90 percent back, and he'd needed only four of the six shots." The pair began training over jumps again in January 2010, and Dario Z has had no more difficulties with that joint since.

"I would definitely recommend IRAP therapy, based on my experience," says Clara. "It brought my horse back. I also like the idea that it's healing with products from their own bodies, not introducing something foreign. It's taking what already naturally works and helping it to work better."

Circle Oak Equine Sports Medicine and Rehabilitation in Petaluma, California, "Horses often were retired or put on masking agents for long periods of time." Now, she says, "some horses are able to perform at a higher level than was previously thought possible."

The procedure is fairly expensive, at \$1,000 to \$1,200 for processing the sample, plus another \$150 or so per injection, for an average total of around \$1,500 for the full course of treatment. However, the improvement in a horse's soundness generally lasts well over the long term, says Frisbie, and the treatments do not need to be repeated more often as compared to other joint injections.

Because of the costs and the time involved, IRAP therapy is generally not a first choice veterinarians offer for a horse with osteoarthritis. Instead, the treatment is reserved mainly for those that have not responded well to corticosteroids, phenylbutazone and other less invasive or less expensive therapies.

Schlachter also recommends IRAP for equine athletes who compete in events that require testing for performance-enhancing drugs, including steroids. "It allows treatment closer to the event without drugs," she says.

LIMITATIONS AND RISKS

IRAP therapy is not appropriate for every horse. Although it can prevent the degradation of cartilage in an inflamed joint, it has a very low success rate in helping horses with advanced osteoarthritis—where the cartilage and bone are already heavily damaged, and torn cartilage, bone chips and other debris are present. In cases like these, says Reinecke, "the clinical effect may be short lived or not there at all."

Risks and side effects from IRAP therapy are relatively low. Because the

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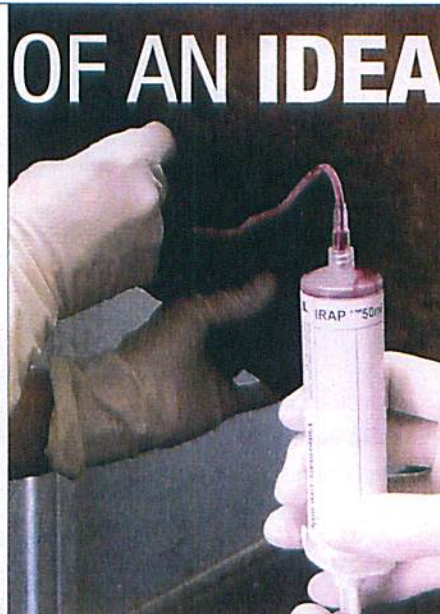
EVOLUTION OF AN IDEA

The concept of treating arthritis by enhancing the availability of interleukin-1 receptor antagonist protein (IL-1ra) in the joints was first developed in the mid-1990s, when researchers Christopher Evans, DSC, PhD, now of Harvard Medical School in Boston, and Paul Robbins, PhD, of the University of Pittsburgh, developed a method using gene therapy—the alteration of a cell's genetic material—to stimulate the cells within a joint to produce more IL-1ra and reduce pain and inflammation in human patients.

"It was performed in 1996 and '97 both in the U.S.A. and then in our group in Germany on human patients suffering from rheumatoid arthritis," says Julio Reinecke, DVM, PhD, managing director of Orthogen AG in Düsseldorf. In 2000, Wayne McIlwraith, BVSc, PhD, and David Frisbie, DVM, PhD, of Colorado State University, began publishing papers on the use of gene therapy to stimulate the production of IL-1ra in horses. In their trials, the technique led to significant reduction in the horses' discomfort and seemed to slow the progress of arthritis more effectively than standard treatments. Plus, it didn't produce any clinically relevant unwanted side effects.

Despite the promising results, the technique wasn't yet ready to be offered in day-to-day practice: "One of the biggest challenges facing gene therapy today is the improvement of current vectors [the methods of delivering genes into the target cells]," they wrote in a paper published in the 2001 Proceedings of the American Association of Equine Practitioners Annual Convention, "and this area continues to be the major limiting factor in gene therapy applications."

Meanwhile, however, Reinecke and colleagues Peter Wehling, MD, and Klaus-



In the 1990s, researchers developed a method of using gene therapy to stimulate cells within a joint to produce more IL-1ra.

Peter Schultz, MD, had developed an alternative method of delivering large quantities of IL-1ra into a joint—by stimulating a blood sample to produce the protein. The method, marketed under the brand name Orthokine, by Orthogen AG, was first used to treat people in the late 1990s. "The first horses and dogs were treated around 2001 [in Europe and Dubai]," says Reinecke.

The good results achieved overseas led to interest in this new method—called IRAP therapy when used in horses—being brought to the United States in 2004. Frisbie led a study, published in 2007, which showed that the method was effective in treating arthritis in horses, and IRAP therapy has been growing in use in this country ever since. In 2009 another version of the IRAP therapy method, IRAP II, was introduced by Arthrex Vet Systems in Bonita Springs, Florida. This system is similar to the original IRAP technology except that



it uses borosilicate beads. One study, accepted but not yet published in the *Equine Veterinary Journal*, showed that IRAP II produced a "moderately better" cytokine profile compared to IRAP when the serum samples were analyzed in a laboratory, according to Frisbie, but clinical differences in live animals have not yet been tested.

The gene therapy and IRAP techniques are not equivalent: The gene therapy approach produced much higher concentrations of IL-1ra in the synovial fluid within the injected joint, and the effects lasted much longer. "The IL-1ra gene implanted into the joint may keep the IL-1ra levels on a constantly high level for weeks or a month to come, while IRAP is subject to weekly injections and therefore fluctuating concentrations," says Reinecke. "The results published by Frisbie and his team do suggest that IL-1ra gene therapy is superior. However, it is currently not available on a routine clinical basis."

Perhaps someday it may be. Evans, Robbins and other researchers are continuing to explore the use of gene therapy to increase IL-1ra in people with rheumatoid arthritis, and in a 2005 paper they wrote, "Promising preclinical data have been obtained for gene therapy of other inflammatory and autoimmune diseases, as well as osteoarthritis and a variety of orthopaedic conditions."

And Frisbie and McIlwraith are also working toward advancing the use of gene therapy for arthritis in horses: "We are pursuing a vector that will produce IRAP longer in the joint than we did in that early work," Frisbie says.

For now, however, the IRAP model using autologous conditioned serum is already helping preserve soundness in thousands of horses with osteoarthritis.

COURTESY, MATT RANDALL, DVM

CASE STUDY: A ONE-TWO PUNCH

Being married to a veterinarian, says Tanya Randall, sometimes means your own horse gets to be a guinea pig for new therapies.

IRAP therapy hadn't been available very long in the United States when Gallant Cashinova (called Emmitt) came up lame in the left hind pastern in early 2006. The Quarter Horse gelding, used for barrel racing and team roping, was only 6 years old.

"We aren't sure what he did to injure himself," says Randall. "He came up sore on the pastern during the previous fall but recovered with rest. We didn't do a lot of competing over the winter, but when I went to start running him he came up sore again. Not long before the lameness became evident, we had helped some friends pen cattle in very steep terrain, which may have been the final straw."

X-rays and ultrasounds showed the extent of the injury, which was in the pastern[®] joint. In addition to inflammation (desmitis) of the medial[®] collateral ligament, which holds the joint together, several of the ligaments around the joint were pulling away from the bone (enthesopathy), and bone spurs (osteophytes) were forming at several attachment points. The resulting instability was leading to arthritis—a classic case of high ringbone.

"Once we felt we had an accurate diagnosis, IRAP was in the first line of treatment," says Matt Randall, DVM, who at the time was at Peninsula Equine in Menlo Park, California, but now practices at Collier Equine Vet Service in Waller, Texas. The therapy wasn't well known at the time, but, he says, "The theory behind IRAP sounded promising. Being able to minimize inflammation and potentially increase the growth factors in the joint



HEALING: Barrel racer Gallant Cashinova's high ringbone responded well to IRAP and extracorporeal shock wave therapy.

should have a better long-term prognosis. And given the significant arthritic changes on the x-rays I was not very optimistic that corticosteroids and other treatments were going to be sufficient."

Because Emmitt had changes both in the joint and at external ligament attachment points, he was treated with both IRAP and extracorporeal[®] shock wave therapy (ESWT) for the soft-tissue injuries. The IRAP was injected into the joint at two-week intervals, for a total of three injections, and the ESWT was done at two-week intervals on the alternate weeks.

"The joint fluid showed some improvement by the second injection," says Randall. "Initially the fluid was quite thin, but by the second injection the fluid was more viscous and had better color. By the third injection what little fluid I got back appeared normal." Follow-up images at six weeks showed improvements in the osteophytes and enthesophytes as well as the medial collateral ligament.

Emmitt had the summer off. "I mainly conditioned him over the following fall and winter," says Tanya Randall. "He started back in competition in the spring of 2007 and has never looked back. People don't believe me when I tell them he has ringbone. You have to feel the pastern to tell."

serum used in IRAP therapy is drawn from the horse's own body, the number of adverse reactions is low—the immune system already recognizes the serum and will not launch an inflammatory or allergic response. However, Frisbie estimates that the rate of "flare"—a sudden increase in discomfort with or without swelling—after IRAP treatment is from 8 to 12 percent, comparable to that found in treatments with other biologic proteins. In addition, says Schlachter, "This treatment carries some risk because we are passing a needle into a joint." Any injection, but

Because the serum used in IRAP therapy is drawn from the horse's own body, the number of adverse reactions is low—the immune system recognizes the serum so it doesn't launch an inflammatory or allergic response.

especially into a joint, carries a risk of infection, from contamination of the entry wound.

To help you decide whether to pursue IRAP therapy with your horse, advises Reinecke, "talk to the nearest veterinarian who has the most experience with the method. Only she or he will be able to make a sound judgment about the probability of success."

As long as we ask horses to run, jump, spin and put in the miles for us, inflammation and osteoarthritis will always be a problem. But IRAP, and other new treatments that may yet come, will go a long way toward keeping horses sound and healthy for life. 🐾

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