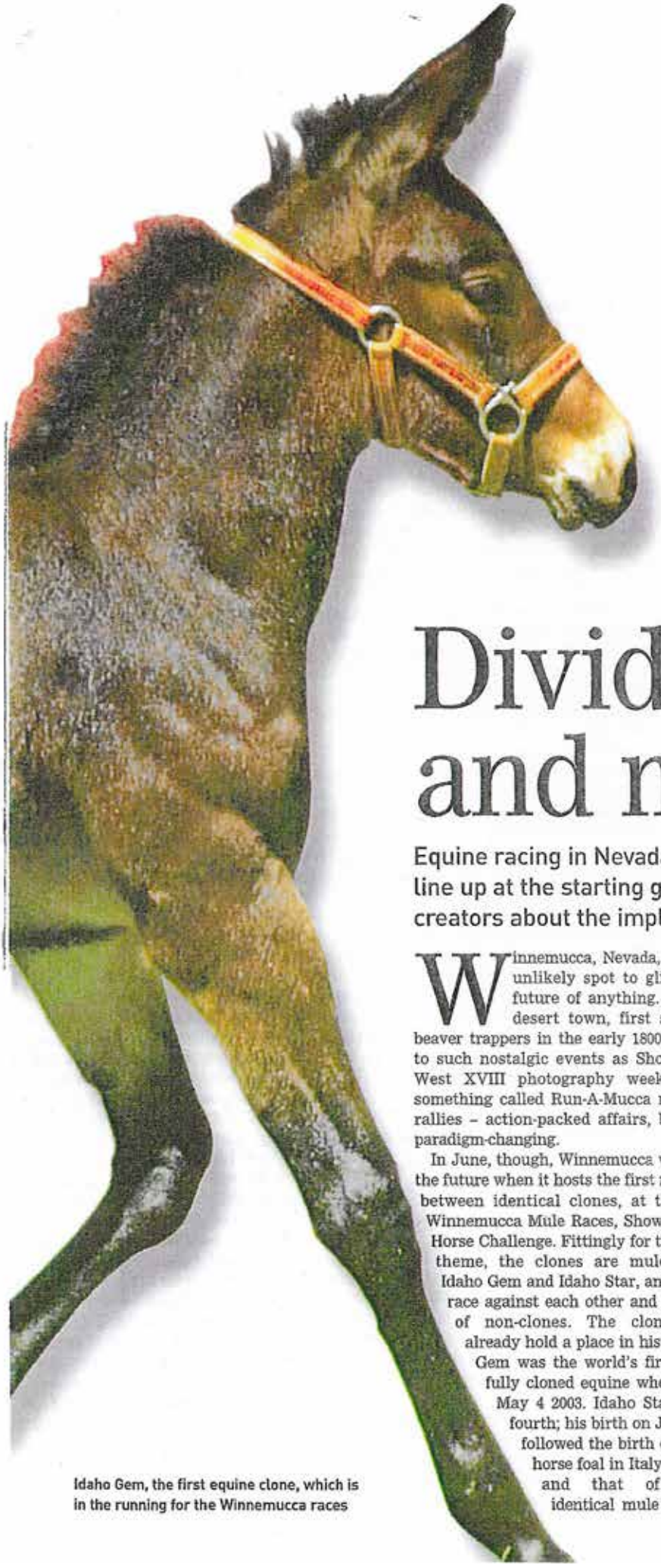

Idaho Gem, the first equine clone, which is in the running for the Winnemucca races

Divide and mule

Equine racing in Nevada will make history when two clones line up at the starting gate. Rachel Pagones talks to their creators about the implications for sport – and human health

Winnemucca, Nevada, seems an unlikely spot to glimpse the future of anything. The high desert town, first settled by beaver trappers in the early 1800s, is home to such nostalgic events as Shooting The West XVIII photography weekends and something called Run-A-Mucca motorcycle rallies – action-packed affairs, but hardly paradigm-changing.

In June, though, Winnemucca will look to the future when it hosts the first race staged between identical clones, at the annual Winnemucca Mule Races, Show and Draft Horse Challenge. Fittingly for the western theme, the clones are mules, named Idaho Gem and Idaho Star, and they will race against each other and a full field of non-clones. The cloned mules already hold a place in history: Idaho Gem was the world's first successfully cloned equine when born on May 4 2003. Idaho Star was the fourth; his birth on July 27 2003 followed the birth of a cloned horse foal in Italy on May 28 and that of another identical mule "brother", Utah Pioneer, on June 9. A handful of horse clones have been produced since.

Mules are great natural candidates for cloning, if not for racing. The product of a female horse and a male donkey, a mule has an odd number of chromosomes, 63, compared with 62 for a donkey and 64 for a horse. As a result, they cannot, as a rule, reproduce. As far as racing goes, with their long ears, stubby tails and notoriously willful attitudes, they are faster than Arabians or Appaloosas but slower than quarter horses (a popular full-size breed, very fast over a quarter of a mile) or thoroughbreds.

There aren't enough racing mules to make up a full day's entertainment, so mule races are often run as the last "feature" race on a day of mixed-breed racing. Nonetheless, mule racing has gained a following at fairgrounds throughout western states, mainly California. Prize money is worth about $5,000 per race and, with only 60 to 70 mules on the circuit, the American Mule Racing Association website may be accurate when it says: "It pays to own a racing mule!"

Although it will be a historic first, the race in June has not been much publicised outside mule-racing circles. I happened on

the news when conducting a telephone interview with Peter Kagel, who was starting up an online horse-cloning business in San Francisco. Kagel has a contract with the University of Idaho scientists who cloned the mules and, almost in passing, mentioned the race. I was instantly hooked because I could see that the race had the potential to be far more than a novelty. Traditional horse breeding and rapid scientific advances in reproduction are on a collision course, and the first shockwaves could be felt, of all places, in Winnemucca.

While doing some preliminary digging into the cloning story, I found an intriguing offshoot. While coaxing the cloned cells to develop, one of the Idaho scientists found a link to the way cancerous cells spread – and possibly a means of slowing or stopping that process. Gordon Woods, a professor in the University of Idaho's department of animal and veterinary science, would tell me later that this discovery was "exponentially more exciting" to him than the birth of the first cloned mule.

Before meeting Kagel and the professors, I called Don Jacklin, an Idaho businessman. Jacklin is the president of the American Mule Racing Association and the visionary behind the mule-cloning project. For him, the race will be the culmination of a dream begun in 1997. That was shortly after the birth of Dolly the sheep, the world's first cloned mammal, at the Roslin Institute in Edinburgh, Scotland. Jacklin had been funding research into animal reproduction at the University of Idaho since 1987. When Woods suggested to him that the cloning itself could be done in Idaho, Jacklin was one step ahead of him. As Woods told me, Jacklin said: "We're going to clone the world's first equine. And by the way, it's going to be a mule."

Jacklin is a man who makes things happen. He was instrumental in developing mule racing from a fringe spectacle held on the dusty margins of western fairgrounds into a public-betting sport with commensurate prize money. Four years ago, Jacklin's champion mule Taz competed in a match race at Del Mar, California's premier racecourse. The race was worth $10,000; Taz was ridden by "Cowboy" Jack Kaenel, who won the Preakness Stakes on Aloma's Ruler in 1982. Unfortunately, Taz was beaten by the legendary Black Ruby.

Idaho Gem and Idaho Star are Taz's brothers. They are not cloned champions. They were created from a foetal cell line which came from an embryo produced by the same female quarter horse and male donkey that, through natural methods, had produced Taz. Because the embryo never developed to maturity, there is no identical adult animal with which to compare them.

In part because he provided the original cells, the cloning project was "something very dear to me", Jacklin told me in a telephone conversation from his home in Post Falls, Idaho, shortly before leaving to go hunting in Mongolia. Another reason is his lifelong interest in the vagaries of DNA. He is an identical twin, and has an educational background in the genetics of plant breeding. The founder of a turf seed production company that branched into Europe and Asia, he is also an avid sportsman, and discovered mules while on an elk-hunting trip. Mules turned out to be more sure-footed and less skittish than horses; Jacklin fell in love and progressed from the world of pack animals to racing mules.

Jacklin envisions a future in which the thoroughbred and quarter-horse industries change their rules to allow clones to race, and he aims to be at the forefront as part of Kagel's commercial venture.

He is also intrigued by the interplay between environment and genetics. While the mules' genes are identical, their environments have differed from the day they were implanted as embryos into different surrogate mares. The clones' paths will have diverged further by the day of the race. They are being prepared in separate locations by different trainers, a deliberate twist on the old debate of nature versus nurture. "We'll have a great opportunity to measure the environmental factor," Jacklin said. "Even though they're genetically identical, the odds of them having a dead heat are like a million to one." Equine geneticists say that only about 35 per cent of racing ability in horses is heritable. That leaves a lot of environmental leeway, even between clones.

While the mules' genes are identical, their environments have differed from the day their embryos were implanted

To Kagel, the mules are part of a revolution in horse racing. Kagel is the president of horsecloning.com, an online commercial venture that has an exclusive contract with the University of Idaho cloning team. Born in Berkeley, California, the 63-year-old is a self-proclaimed child of the revolution. A practising litigation lawyer, he once sued the California Bar Association to allow him to use its magazine to advertise his "Lawyer's Brain" T-shirts, depicting a cartoon map of legal grey matter in which thoughts of sex and deception occupied the largest areas. Kagel won. He met me at San Francisco International Airport in a circa 1979 robin's-egg-blue Mercedes. Midday traffic into the city was heavy, and idling behind a hybrid-fuel vehicle sporting a "Drop Bush Not Bombs" bumper sticker, he launched into a critical dissection of the current administration.

He sees horse racing as one more example of society in need of a revolution. The exclusive policies of the Jockey Club, which in America is the thoroughbred's record keeper and in Britain is the sport's ruling body, are anathema to him. "I'll say one thing about the Jockey Club – they are a club," Kagel says as we cruise into the Haight-Ashbury district. "All racing is just a club and they're trying to protect it through exclusion. You have to believe the market will fill needs." He believes that the traditional economics of breeding, in which the breeder pays the stallion owner a fee for covering (breeding with) his mare, will be replaced by a system of royalty negotiation as each clone is patented.

Kagel's vision of horse racing, which he has posted on his website, is a mixture of futuristic fantasy and a startlingly accurate portrait of racing's present woes. It says in part: "An entrepreneur will step up to the plate and produce made-for-television-races pitting clones, even identical clones, against each other that will draw huge television audiences because people want to see the fastest and legendary horses race. Betting will occur on the internet through the numerous offshore gambling websites. Fans will stay away from the tracks in large numbers. The track owners will realise that they have been relegated to minor-league status and then, facing a substantial lack of revenue, will embrace cloning and the Jockey Club rules will be changed."

Kagel does a pretty good job of describing the present state of racing. Betting already occurs on the internet, and fans are staying away from the track in large numbers. Many track owners know they face minor-league status; in the US, one response has been to install on-track casinos.

There are, arguably, good reasons to clone – recreating a top gelding such as

PHOTOGRAPH: AP

Best Mate for breeding purposes, for example. But Kagel's main stumbling block will be the breeding industry. Thoroughbred breeding is based on a tradition that has changed little since the first edition of the *General Stud Book* was published in Britain in 1791. No recognised thoroughbred racing authority in the world allows horses produced by methods other than natural cover to compete.

The traditional thoroughbred breeding industry's arguments against cloning range from visceral reactions – one breeding organisation executive told me it was "like Hitler trying to create a master race" – to the rather bizarre contention that only the vigour of natural cover can engender a champion's drive to win. But the simplest explanation for such opposition is that the biggest stallion owners benefit massively from the status quo, in which they control the numbers of foals their charges produce.

By manipulating hormone levels and other practices, stud managers are able to mate their most commercially popular stallions with more than 200 mares in a season. The most expensive stallion in the US, Storm Cat, covered 116 mares in 2004. The fee to breed a mare to him is $500,000. With profits on this scale, the vested interest is clear.

After leaving Kagel, I flew to Spokane, Washington. The road from Spokane to Moscow, Idaho passes through 90 miles of America's heartland. The scenery is rolling wheat fields, brown after the harvest. Pick-up trucks fly the American flag from their side view mirrors. Woods and his colleague and former PhD student Dirk Vanderwall work in a low brick building across the road from Moscow's only strip mall. With Kenneth White, a former college football star and reproductive physiology expert from Utah State University, they worked for four gruelling years to create the clones. They've been through a lot together, and complement one another easily.

Vanderwall is the frontman; always available, he answers e-mails promptly and leaves a detailed message on his phone as to when and how he can be reached. Woods is more elusive. However, it was Woods who arrived first for a breakfast interview in the Best Western, dressed crisply in a dark suit, pale blue shirt and red tie. Vanderwall came dashing in a few minutes later, wearing a red fleecy top, a jumbo-sized cup of coffee in his hand.

I put aside my questions when the scientists began retelling the story of Idaho Gem's birth. As they talked, it became clear that this was more than a professional accomplishment to them; it was one of the most important moments of their lives, and they spoke of it with the wonderment of new fathers. They are both fathers and Woods, after describing the birth of his youngest child, whom he helped deliver in a Delaware hospital, says: "Idaho Gem's birth was almost – *almost* – on a par with that."

Idaho Gem's birth was one of the most important moments of the scientists' lives. They spoke with the wonderment of new fathers

Knowing their work was controversial, they took precautions. The pregnant surrogate mares were moved to a secure off-campus location. But they knew that problems could occur late in pregnancy with any equines, and that cloned cattle were often born with severe abnormalities. "When he [Idaho Gem] just stood up, after a natural and unassisted birth, it was a huge, huge relief," says Woods.

It was 3am and Vanderwall was collecting samples of everything. "He poops, we got it. He urinates, we got it," recalled Woods. "But it wasn't overkill – I mean, everything he did was monitored." Later, DNA tests would verify that this was a cloned mule. But Woods, who wanted to be sure at the time, asked himself: "How long are the ears and is it a male? Those were the two things – you need to be the same sex, and you need to have long ears. And if it had those two things, then it was in fact the world's first cloned mule."

I asked about the ethical implications of the clones in a conservative state such as Idaho. Woods, who described himself to me as "spiritual" before revealing that he is a Mormon, has given the matter close thought. "I remember when I first collected an embryo from a mare, I looked at the embryo and I thought, is this going to adversely affect the health of the offspring? As a veterinarian, I'm committed to animal health, and I didn't want to produce an animal that would suffer. And when the animals were healthy and vibrant and just dancing around – well, I haven't had any feelings that there's anything wrong."

But the public still needed convincing, so the team took their mules on the road. One of the main stops was the American Association for the Advancement of Science conference in Seattle, Washington. With a team of students driving the livestock – "We're at a university here, so let me tell you our budget is austere" – they arrived with fanfare and monopolised media attention in the convention centre. From Seattle to Blackfoot, Idaho, they found immense curiosity, but surprisingly little resistance to the idea of cloned animals. They were prepared for dissent, even sabotage, but there was a little of the former and none of the latter. "I got a couple e-mails – just a couple – and one e-mail said, 'I'm Satan, thank you very much', and I thought 'Whoa!'," Woods says. "But bad things have not happened."

Nor has religion caused a conflict, at least not the Mormon religion, which dominates Utah and parts of Idaho. "I've never had anybody from the Mormon church take me aside and say, look, you shouldn't be doing this," says Woods. "When we were in Blackfoot – that's a Mormon community – there were these 80-year-olds that came in. They were very conservative by many standards. They wouldn't drink alcohol, that sort of thing, and they were very traditional on family values. I mean we were talking grandma and grandpa. We were talking the ultra-conservatives out of that conservative group. But they came in and when they saw the healthy animals combined with the application to human health, they were totally supportive of that."

Ah, the application to human health. The true revolution engendered by the clones may be in human medicine rather than thoroughbred or mule racing. Before explaining it, Woods invited me into his office, an unnaturally tidy room. The only personal touch was a framed poster of Einstein with the quote: "Great spirits have always encountered violent opposition from mediocre minds."

Woods is leaving the commercial cloning project to Vanderwall, Kagel and Jacklin, while he pursues a related application to human cancer. That work began at about the time Jacklin first envisioned a race with cloned mules. It finally came together during the cloning experiment, and the key to successful cloning also turned out to be the key link to cancer.

Earlier attempts by the Idaho scientists to produce a horse through in vitro fertilisation had failed miserably. Although more than a million human babies have been conceived using the procedure since Louise Brown's birth in 1978, the method was not working with horses. The problem was that the embryonic horse cells were not dividing. Woods formed the hypothesis that horses have low cell activity compared with

humans. The implications went way beyond cloning. "There's an electrifying similarity between rapidly dividing embryo cells and rapidly dividing cancer cells," he explained. "And we thought that if in fact horses have a lower cell activity, we would expect the cancer mortality to be lower in horses than in humans." That proved to be true. Using data from the University of Kentucky, they found that cancer mortality in horses was 8 per cent, compared with 24 per cent in humans. And prostate cancer had never been found in stallions, which have a prominent prostate gland.

The team began looking for a chemical explanation. Woods believed that if they could identify the activation chemical, which was lower in horses than humans, they could use it in the cloning programme to override the slow division of the embryonic cells. Cellular calcium levels proved to be the key, and once the team began manipulating cellular calcium, they were on their way to a successful clone.

"Calcium in a cell regulates every cell activity," Woods explained. "We identified calcium to be higher in stallions than in men in the extracellular fluid. And this initially was really disturbing, because we expected a lower concentration." Woods remembers precisely the day that he solved the puzzle. It was New Year's Day, 2001. "This was for me one of the most exciting moments ever in my scientific career."

A flash of insight told him that the calcium concentration was higher in the extracellular fluid but lower inside the cells of the horses than those of the men. "From a reproduction standpoint, that's bad," Woods said. "But from a disease standpoint, the horse has got its system set up to be super healthy."

Using standard calcium concentrations, the team transferred 130 embryos into surrogate mares; two of them lasted to 14 days, but neither made it as far as 30. But when they increased the concentration three-fold, "right off the bat we got three pregnancies from 40", Woods says. "And what was exciting was that two of them developed out to day 30 and in one we picked up a heartbeat. When we first saw that heartbeat on the first transfer, we knew we had it. We just had to stay with it."

Two years later, the three mule foals were born, and Woods went back to his blackboard. Using data collected in 2000, he looked at the levels of prostate specific antigen in a group of men. PSA is a marker for prostate health; high PSA is correlated with prostate cancer. Extracellular calcium turned out to be lower in the men with the higher PSA levels, while their cellular calcium was higher.

The challenge was to figure out why. The team identified a chemical that increases the movement of calcium into the cells and a counterbalancing "chemical x", which acts as a blocker. As its presence decreases, it allows more calcium to enter the cells, leading to higher cell activity. And chemical x decreases in humans as they age.

The idea that one man's dream to race cloned mules could lead to another's dream to develop an effective new cancer treatment is compelling. While we were still at breakfast, Woods told another story. "There was a scientific panel that I participated in, and the story that I shared was very simple. One was that the animals were healthy – extremely healthy – and the second is that there's an application to human health. And at the end of it a man (he was arguing with everybody) stood up and said, 'I went out and talked to the students, and they said the reason you cloned the mules was to be the first in the world to clone an equine. And now I listen to you, and you say the reason you cloned the mules was to test the scientific hypothesis relating to human health.' He said: 'Which is it?' And I said: 'Yes'.

"He gave me this look, and it was almost like we were speaking a different language, and it seemed like everybody in the audience got it but him. But it was shared objectives, and that's been one of the really fun parts of this project. I think each one of us on the team has come into it with a slightly different objective, but we've all come together. Don Jacklin has his drive on it, which is not to test a scientific hypothesis. He understands the hypothesis, he's supportive of it, but I don't think he would have antied up the money for that reason."

The story is not over. Kagel is drumming up clients in California, Jacklin is avidly following the mules' training progress and Woods has formed a company to pursue the cancer research. Perhaps none will fire up a real revolution, but it is hard not to believe that they have already forced the strange and uneven march of progress another ineluctable inch forward. FT

Rachel Pagones is bloodstock editor of the Racing Post.

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Equine Cloning May Shed Light
On Human Cancer Causes

MOSCOW, Idaho – The same chemistry that led to the successful cloning of a mule at the University of Idaho this month also may shed new light on the causes of specific cancers in humans.

According to UI Professor of Animal and Veterinary Science Gordon Woods, leader of the UI-Utah State University team that recently produced the first mule clone, the chemical changes necessary for the successful cloning provide new insight about what influences cell growth and activity. In addition, Woods, who also serves as director of the UI's Northwest Equine Reproduction Laboratory, said the horse provides a novel and effective model for studying cancer metastasis and other age-onset diseases in humans.

"The mortality rate for horses with metastatic cancer is 8 percent for all cancers and 0 percent for prostate cancer. By comparison, the mortality rate in humans is approximately 24 percent for all cancers, of which 13 to 14 percent are for prostate cancer," Woods said. "The contrasts and similarities between humans and horses at the cellular level provide a number of insights about how the relationship of certain chemicals in the body affect both normal and abnormal cell activity."

Calcium – more importantly, the relationship between the amount of calcium within each cell and outside each cell – is key. Members of the horse family have a lower amount of intracellular calcium than humans and a correspondingly slower rate of cell activity.

Woods said when his team first started its cloning work in 1998, only a very few of the implants resulted in pregnancies, and none of those progressed past the four-week point. Based on new information provided by CancEr2, a private corporation founded by Woods, the scientists agreed part of the problem was the relatively slow rate

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of cell activity in members of the horse family. Woods noted that the slow rate of cell activity may be why in vitro fertilization doesn't work in horses and may be why the cancer mortality rate among horses is so low.

In July 2001, however, the team supplemented the amount of calcium in the implanted clones. "We increased the calcium in the medium holding the embryos and saw a seven-fold increase in our week two pregnancy rates," Woods said. "We produced 19 pregnancies; the first baby has been born, and two more pregnancies are in the advanced stages."

The team concluded that the increase in calcium within the implanted clone cells directly impacted the speed of cell division. Understanding the role of calcium in equine cell activity was a direct result of work conducted by Cancer2. Cancer2 gifted the intellectual property to UI.

According to existing research, the amount of intracellular calcium is higher than normal in humans with metastasizing cancer. According to Woods' research, the amount of intracellular calcium is below normal in horses. Within Cancer2, Woods and his team have discovered a chemical that suppresses intracellular calcium. Abnormally high intracellular calcium is a root cause of abnormally high cell activity in aged humans.

"There are electrifying similarities between cancer metastasis and embryo division," said Woods. He said he is working toward critical testing of the effects of deficiencies in the suppressor in human clinical trials. "We've identified a suppressor of intracellular calcium and believe its deficiency is the root cause of abnormally high intracellular calcium."

Woods established the Northwest Equine Reproduction Laboratory on the UI campus in 1986. He had come full circle, having completed pre-veterinary courses at the UI in 1974. A few years later, he earned the D.V.M. degree from Colorado State University.

Woods returned to the Northwest briefly to practice veterinary medicine then moved east to complete a residency in large animal reproduction at the University of Pennsylvania under R. M. Kenney. Next, at the University of Wisconsin, he became a student of O. J. Ginther, and completed his master's and doctor's degrees under his direction.

Woods' first faculty assignment came in 1983 at the New York State College of Veterinary Medicine where he originated and directed Cornell's Laboratory of Equine Embryo Biology. He left Cornell in 1986 to set up the Northwest Equine Reproduction Laboratory on the UI campus.

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