

Matrix

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Ellison Institute poised for preeminence

In the Silicon Valley, Lawrence J. Ellison found everything he needed to build a new software idea into a Fortune 500 company. But when the self-made computer billionaire shattered his left elbow in a 1992 bicycle accident, he had to go to the Central Valley to find a surgeon with the skill to repair it.

At UC Davis Medical Center, Department of Orthopaedics Chair Michael W. Chapman reconstructed Ellison's elbow in a series of two operations, restoring the badly fractured joint to full function. When Ellison, 52, recently challenged world-class triathlete Peter Kain, 32, to a "bar dip" contest to benefit a charity, Ellison won. He did 49 of the pushup-like exercises to Kain's 40.

"All the king's horses and all the king's men couldn't put Humpty together again," a grateful Ellison said after his final operation. "But Mike Chapman could. And did."

Ellison, co-founder and chief executive officer of Oracle Corporation, expressed his thanks with a \$5 million gift to support musculoskeletal programs at the UC Davis School of Medicine and Medical Center. The gift, matched by a \$1.3 million UC Davis Health System contribution, represents the largest single private bequest in the institution's history.

"I wanted to make the art and science of Mike Chapman and his colleagues generally available, instead of available only to the few," Ellison said in announcing his 1994 bequest. "I wanted more people to be able to benefit."

They soon will. The Lawrence J. Ellison Neuromusculoskeletal Institute, a newly designated UC Davis Health System Center of Excellence, is evolving into one of the preeminent clinical and research centers for connective tissue disorders in the world. The Institute brings together under a single umbrella patient care and research programs within several departments, including orthopaedics, physical medicine and rehabilitation, neurology and neurosurgery, radiology and nuclear medicine. In addition, Institute

clinicians and investigators will coordinate their efforts with other departments that pursue musculoskeletal research, including the Veterinary Orthopaedic Research Laboratory, the Otolaryngology Research Laboratory, the Division of Materials Science, the Biomedical Engineering Graduate Group and the Departments of Physical Education, Civil Engineering and Mechanical and Aeronautical Engineering.

"Combined with the resources of the Medical Center, the new Shriners Hospital, the School of Medicine, other centers on the Davis campus and the UC Davis Orthopaedic Research Laboratories,

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After a full recovery from a shattered elbow, computer billionaire Larry Ellison (far right) beat triathlete Peter Kain (middle) and Jim MacLaren in a charity weight lifting contest.

New clinical programs

The Neuromusculoskeletal Center of Excellence will encompass at least 16 separate clinical programs.

The programs will be housed together in the Lawrence J. Ellison Ambulatory Care Center, due to open next summer. Their aims will be to increase communication and collaboration among the varied specialists who treat a particular disease or disorder; to streamline patient referrals and care; and to facilitate comprehensive, prospective outcomes studies.

"Patients now have to go to one place for one thing and another place for another thing, requiring multiple appointments and inhibiting interdisciplinary communication among treating physicians," said center chair Ralph Johnson.

"This can be resolved by having a program with a coordinator who can bring it all together, and by housing services in a single building so that the patient comes to one place for a thorough evaluation and treatment."

The Spine Care Program, which opened May 1, was the first to begin seeing patients under the aegis of the new Center of Excellence. Southern California spine surgeon Munish Gupta has been recruited to head the program. According to Johnson, the program will bring together surgical and nonsurgical health professionals skilled in the diagnosis and treatment of a broad spectrum of spine

Connective tissue research, repair a focus

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the Institute should eventually provide us with the biggest critical mass of investigators in the molecular and cellular biology of connective tissues anywhere in the world," Chapman said.

The Institute will specialize not only in orthopaedic problems like Ellison's shattered elbow, but also in muscular and neurologic disorders stemming from such diseases as cerebral palsy, multiple sclerosis and stroke.

"We're excited about it," said Ralph Johnson, acting chair of the new Center of Excellence. "It will bring together the competence of those departments and specialists who care for neuromuscular and musculoskeletal disease, provide comprehensive care to patients and offer both new research opportunities and new opportunities for evaluation of treatment outcomes."

Three new endowed chairs constitute the centerpiece of the Institute. The Lawrence J. Ellison Chair in Musculoskeletal Molecular Biology, assumed April 1 by A. Hari Reddi, is endowed with \$2.7 million from the Ellison bequest and \$500,000 in UC Davis Health System matching funds.

The other chairs will be activated when the ribbon is cut next summer on The Lawrence J. Ellison Ambulatory Care Center. The David Linn Chair in Orthopaedic Surgery, named for Ellison's brother-in-law, will support the Chair of the Department of Orthopaedics. Its endowment includes \$1.3 million from the Ellison gift and \$300,000 in Health System matching funds. The Doris Ellison Linn Chair in Bone Biology, named for Ellison's sister, will support research at the Orthopaedic Research Laboratories. It carries a \$1 million endowment from the Ellison gift.

Rather than paying the salaries of incumbent faculty who assume the chairs, the David Linn and Doris Ellison Linn endowments will be used to support additional post-doctoral fellows, graduate students, technicians, equipment and supplies in orthopaedic research.

R. Bruce Martin, director of the Orthopaedic Research Laboratories, predicts the endowment

"Thanks to this gift, we have the potential within 10 years of having a research program in musculoskeletal and neuromuscular biology here at Davis that will be unmatched. It will make available to the citizens of our region a level of care that is unparalleled and provide them with access to the most recent advances as they come along."

funds will elevate the lab "to the first rank of such laboratories in the world." The lab's primary focus has been trying to understand how bone, cartilage, tendon and ligament cells continually renew and repair themselves as they adapt to the changing demands of daily activities.

Once this fundamental mystery has been solved, investigators will have a means of healing and preventing connective tissue diseases, from arthritis to osteoporosis. "Ultimately we may learn to reconstruct the skeleton biologically rather than with carpentry," Martin said.

It took master carpentry to repair Ellison's bicycle injury. The software magnate suffered an intraarticular T-type supracondylar fracture of the humerus, complicated by loss of motion in the elbow.

Ellison's Bay Area orthopaedist, a member of a prominent sports medicine practice that provides team physicians for the San Francisco 49ers, promptly referred the complicated injury to Chapman, an internationally renowned traumatologist.

In one operation, Chapman fixed the fracture with plates and screws. In a second surgery, he removed the hardware and

performed a soft tissue release that restored the joint's function.

"He got essentially a perfect result — an almost unheard-of outcome," Chapman said, attributing Ellison's spectacular recovery in large measure to Ellison himself. The same drive and determination that took Ellison to the top of the software business carried him through the painful, months'-long rehabilitation process. During that ordeal, Ellison first proposed making a gift to the Department of Orthopaedics.

Ellison has a history of backing winning ideas. Born in New York City and raised in a tenement on Chicago's South Side, the son of Russian Jewish

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New building centralizes multispecialty care

For patients seeking care at UC Davis Medical Center, the Lawrence J. Ellison Ambulatory Care Center will mean one-stop shopping for services that now require visits to multiple office sites along Stockton Boulevard. For physicians and researchers, the shared space will mean new opportunities for interdisciplinary collaboration. And for the UC Davis Health System, the building will mean a more cost-effective alternative to expensive leased office space.

The four-story, 375,000-square-foot building is rising along 48th Street on the eastern edge of the medical center's 140-acre Sacramento campus. When completed next July, the \$81.2 million building and its 124 exam rooms will accommodate up to 806 patients a day — about 70 percent of all ambulatory patients seen at the medical center.

The expansive facility will also house 250 faculty offices, a visitors cafeteria and an employee food service operation. A new freestanding parking structure, connected to the building by a landscaped breezeway, will provide convenient parking for 800 cars.

"The Lawrence J. Ellison Ambulatory Care Center is the culmination of the Neuro-musculoskeletal Center of Excellence," said Center Director Ralph Johnson. "It will bring together all those departments that deal with neuromuscular and musculoskeletal problems in the same building for clinical evaluation, imaging studies and treatment."


Occupying the basement floor will be the neurology and neurosurgery clinics; the cardiac rehabilitation and cardiology clinics; and an imaging center. On the first floor will be orthopaedics; physical medicine and rehabilitation; occupational and physical therapy; indoor therapy pools; an orthotics laboratory; family practice; the remainder of the imaging center and a pharmacy.

The second floor will

house special procedures and pain clinics; obstetrics and gynecology; ophthalmology; dermatology; urology; plastic surgery; and academic offices for the departments of obstetrics and gynecology, ophthalmology and family practice. The top floor will be home to an Alzheimer's disease clinic and academic offices for faculty in orthopaedics, physical medicine and rehabilitation, neurology and neurosurgery, pain management, urology, dermatology and radiology.

The building also will feature an outdoor wheelchair PAR course designed to teach patients in wheelchairs to negotiate sand, gravel, small bridges and other everyday obstacles.

Named for Oracle Corporation chairman and chief executive officer Lawrence J. Ellison, a former patient and major benefactor, the building is part of a long-range development plan adopted by the UC Regents in 1989.

"The Ellison Ambulatory Care Center is going to change the way we do business," said Ray Groom, manager of medical sciences planning. "A patient will be able to see a physician, get an X-ray or other radiographic diagnostic procedure, fill a prescription and have lunch without ever leaving the building. Literally everything they need will be right there." 



The Lawrence J. Ellison Institute will open in July 1998.

problems, from fibromyalgia to workers' compensation injuries.

An arthritis and total joint replacement program will be the Center's second major priority, Johnson said. Other top priorities are programs in stroke treatment and sports medicine.

A trauma/vascular surgery program will be headed by Paul Muizelaar, new chair of the Department of Neurological Surgery and a nationally recognized vascular surgeon. Muizelaar is bringing UC Davis to the forefront of research into ways to improve the outcomes of people with traumatic brain injury.

Plans are also underway for an anesthesiology/chronic pain management program and a spasticity management program for patients who suffer from chronic, debilitating muscle spasms due to stroke, cerebral palsy, multiple sclerosis and a wide range of other injuries and disorders. Available therapies for these patients include tendon-lengthening surgery and use of an implantable pump to deliver baclofen, a drug that inhibits uncontrolled muscle reflexes.

Johnson is meeting with a committee to identify other clinical programs that may be developed within the Center of Excellence. Ultimately, the Center may encompass as many as 30 programs.

New Ellison Chair studies the mysteries of tissue regeneration

This story begins with a mystery. In 1965, UCLA surgeon Marshall Urist ground up rabbit bones and demineralized them in acid so that only powder remained. When Urist sprinkled the powder into the muscle of a living rabbit, the unexpected happened: new bone started to grow in the muscle tissue.

What was it about the bone powder that could cause muscle tissue to become new bone? For science to be able to take practical advantage of this wonder, someone would have to isolate the specific factor or factors that caused bone to grow.

Finding the answer would take nearly twenty years. And it would deliver into the hands of science an unprecedented power: to regenerate bone and learn the secrets of tissue formation.

The solution of this mystery story has A. Hari Reddi at its center. Reddi, the holder of the new Lawrence J. Ellison Chair in Molecular Biology at the UC Davis School of Medicine and Medical Center, is not the only one who helped solve the mystery. Science is additive and collaborative. But the contributions of Reddi, who comes to UC Davis from an endowed chair at Johns Hopkins, were pivotal.

In his laboratory at Johns Hopkins, and before that at the National Institutes of Health, Reddi struggled with the implications of Urist's results. Reddi persisted at a time in the 1970s and early 1980s when most other scientists had lost interest in what they considered a hopeless quest.

"He kept the field alive," said Vicky Rosen, a biochemist at Genetics Institute, a biotechnology

company based in Cambridge, Mass. Ultimately, the solution would come from the biotechnology industry, but not before Reddi and his colleagues had squeezed clues from the dry bones — clues that would later allow him to embark on an ambitious program of tissue engineering.

In any mystery story, the person at the center has to find his way to the action. In Reddi's case, the journey was particularly long. It began in Madras, in the dusty southern part of India, far to the south of Delhi. Already as a student at Annamalai University in the isolated town of Annamalainagar, 100 miles south of Madras, Reddi knew that he wanted to do research in the United States.

"There was very good research in Madras at the time," Reddi said. "But it wasn't enough. So I decided to travel 1,000 miles to pursue scientific studies at the graduate level in Delhi. Such things were almost never done," he said.

Reddi advanced by learning from a series of successful mentors. His graduate advisor, M.R.N. Prasad, had done research in Wisconsin. "He encouraged me to work independently," in contrast to the more hierarchical style then in vogue in Indian universities.

Reddi's independent thinking paid off. One of the readers of Reddi's dissertation, H.G. Williams-Ashman of Johns Hopkins University, recommended Reddi for the distinction of *magna cum laude*. Soon Reddi was on the way to Williams-Ashman's laboratory for post-doctoral work.

What came next was the move that put Reddi in the right place at the right time for addressing the mystery. In 1969, Williams-Ashman moved to the University of Chicago and Reddi joined him. Down the hall from their lab was Charles Huggins, a powerhouse of biochemistry, who was to win the 1966 Nobel Prize for his work in understanding the endocrine regulation of prostate cancer. Trained as a surgeon, Huggin's rapacious intellect kept bringing new questions and new collaborators into his laboratory. Urist had been a student of Huggins', back in the 1940s, and Reddi would join him.

"But I already have a firm offer to go to Harvard and to return to India after that," Reddi recalled telling him. But Huggins immediately picked up the phone and dialed Reddi's erstwhile mentor at Harvard, saying, "He's not coming!"

"It was a decision that changed my life and my focus of research," he said.

Huggins had planted the seed for Urist's work many years earlier, when he implanted a canine tooth fragment into the abdomen of a dog and showed that



A. Hari Reddi, I

**The experience of
isolating bone induction
factors gave Reddi
unique insight into
tissue formation. In
some ways, bone is an
unusual tissue but in
other ways it is typical.**

new bone formed there. But the mystery was even more baffling than that it would become thirty years later.

Years passed. Reddi became a professor at University of Chicago, then accepted an offer to become a visiting scientist at NIH in Bethesda. Reddi had successes in other areas, especially in characterizing the roles of specific proteins in expanding bones that already existed.

But all along, he remembered Huggins' challenge: What property of the bone powder — or the dog's tooth — was acting like an inducer, causing bone to grow in muscle or abdomen?

Night after night, month after month, Reddi went after the elusive "bone induction factor." His former post-doctoral fellow Kuber Sampath remembers seeing all the notebooks in Reddi's NIH laboratory. "Reddi had spent a lot of time looking for these factors," recalled Sampath, now a senior research director at Creative Biomolecules, a biotechnology company in Hopkinton, Massachusetts.

Part of the difficulty was in not knowing if a single factor was there to be found. Looking for a bone induction factor was "an orphan project" at that time, said Rosen. "No one even believed that there was a factor. They thought it was a mixture of things."

Another problem lay in the nature of bone. Reddi's approach is what he calls classic "grind and find" biochemistry. It involved taking the tissue in question, grinding it up and then sifting through it looking for the activity, in this case, bone induction. In the days before cloning and sequencing of human genes, grind and find was about the only option available.

But it did not work very well on bones. It was difficult both to find potential factors and then to see what effects they had. Finding factors was hard because the scientists had to be so harsh in extracting them — how could they be sure that the acid bath that degraded the bone was not also irreversibly altering the factor?

Observing the effects was difficult because of the challenge involved in putting bone cells in tissue culture. Most cells could be induced to grow in a somewhat normal manner in a tissue culture dish, even though they were outside of their

normal environment. But success in bone tissue culture meant that bone cells would begin to calcify to the bottom of the dish, limiting their own growth. That made it even more difficult to determine what had caused the cells to grow.

Another obstacle, one that had stymied Urist, was that he did not have a reliable assay for quantifying bone growth. The key to "grind and find" lay in knowing what one has found, said Reddi. But the assay problem seemed insurmountable.

When Kuber Sampath told Reddi he wanted to work on finding "bone induction factor," Reddi tried to dissuade him. "Maybe you'd like to think it over," Reddi said. "You might not get any publications." But Sampath persisted and ultimately succeeded at winning Reddi's support.

Sampath's presence reinvigorated the search for the mystery factor. He also brought new methods and new ideas from his background as a protein biochemist. It was a true collaboration, Sampath recalled, free of the usual hierarchy. "Hari never acted as a senior person," a superior, said Sampath. Instead, Sampath and Reddi would talk on the verandah outside Reddi's NIH office.

Over the next five years, "we developed a bona fide assay that reflects bone formation," recalled Reddi with pride. The assay, which is still in wide use, involves implanting a pellet with the mixture to be tested beneath the skin of a rat. In a few days, if the test mixture is active, progenitor cells migrate to the area and bone begins to form. Twelve days later, the implant is removed and the effect of the test mixture is quantified — the key to a scientific assay — by two different measures.

With the assay problem solved, it was time to find the bone induction factor or factors. Unfortunately, the amounts of the active substances were so small that they could not be used to characterize the molecule. "It would have cost too much money," said Sampath. "We would have had to extract the substances from twenty kilograms of bone every week, and the chemicals we used were expensive." In the end, he recalled, it cost tens of millions of dollars to isolate the gene.

That's where biotechnology companies stepped

A. Hari Reddi was recently awarded the Urist award from the(more TK).

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Cartilage implants offer treatment for arthritic knee injuries

The talk is generally called “The middle-aged arthritic knee.” It’s not exactly an award-winning title, but year after year, overflow crowds pack a lecture on this topic at the American Academy of Orthopedic Surgeons’ annual meeting to hear about the latest treatment options.

“The problem is that we see arthritic knees every day, and there is no single treatment that is as good as we would like it to be,” said Juan J. Rodrigo, professor of orthopaedics at UC Davis School of Medicine and Medical Center.

Knee problems in the United States are reaching epidemic proportions. In 1994, the last year that statistics are available, orthopedic surgeons in the United States performed 311,000 knee surgeries, an increase of nearly 50 percent from four years earlier. Hips and shoulders present similar problems and are responsible for increases in the number of surgeries on the three joints, which totaled 649,000 in 1994.

Given that there is no “one-size-fits-all” treatment, a medical center like UC Davis does the best for its patients by offering every available option, said Rodrigo. “We treat patients who are experiencing the early stages of arthritis as well as 90-year-olds who need end-stage treatment revisions.”

Most of the treatments involve cartilage because while bone heals, cartilage doesn’t. Made up of long strands of water-cushioned collagen protein, cartilage is a slippery shock absorber for the bangs and bumps of life. But sometimes it is torn off, as by an injury. Or it can rub away due to arthritis or everyday wear and tear. A long, painful slide into immobility often results.

In an ideal world, physicians would augment worn or missing cartilage with more cartilage through transplantation or regrowth. And that is just the way the medical profession is moving. The trend is toward “true biological replacements,” said Rodrigo. “They offer the potential for remodeling and healing.”

But until recently, the treatment of choice for many patients — especially those 45 years old and up — has been to replace the entire joint with a metal or plastic prosthesis. With the appropriate rehabilitation program, recovery time is quick, said Rodrigo — in as little as three months, patients can resume many of their previous activities. The prostheses can last as long as 20 years.

However, knee and hip replacements have their drawbacks as well. The joints can fail, they can wear out and they can wiggle loose from their moorings. Worse still, said Rodrigo, replacement joints almost inevitably destroy bone and often cause infection. A

second replacement has to be larger for surgeons to be able to fuse it to healthy bone. And the larger implant then reduces the patient’s mobility even further.

When patients are younger than 45, and especially if the problem is caused by a recent injury, Rodrigo typically turns to one of the “biological” treatments — a procedure known as debridement and microfracture (D&M), which could just as well be called “scrape and tap.”

The advantage of D&M is that it provides an opportunity for the patient’s own cartilage to fill in the gaps. With the aid of a viewing device inserted through a periscope-like arthroscope, Rodrigo removes any remnants of cartilage and debrides the bone with a sharp blade. He then uses a second arthroscope to insert needle-like awls with a diameter no thicker than the width of a dime. He uses the awls, which look like tiny ice picks, to poke holes into the bone down to the marrow. After punching 20 to 30 holes, he closes the incision and the real work begins — by the patient through rehabilitation.

But where does the cartilage come from? It grows by itself, said Rodrigo, from precursor cells that ooze from the bone marrow onto the scraped bone surface. Over time, the precursor cells turn into “fibrocartilage,” a replacement tissue that is “not exactly the same as native cartilage but serves the same purpose,” he said.

The advantages of the procedure are simple. “We are just regrowing a tissue that would otherwise not grow,” he said. The success rate for this procedure, which is performed around the country, is about 80 percent. Success is defined as a return of function to within 10 percent to 20 percent of what it was before injury. Compared to the typical 50 percent reduction of function in patients when they come in for treatment, it is a significant improvement.

But D&M has some drawbacks too. The failure rate for regrown cartilage is high — 20 percent to 25 percent in 10 years.

Consequently, many groups are attempting to improve on cartilage regrowth. One of the most advanced efforts, which is being performed on an experimental basis at UC Davis, takes the patient’s own cartilage cells and multiplies them in a laboratory before re-implanting as many as thirty million cells several weeks later.

The treatment, which was first used in Sweden 10 years ago, has a reported success rate of 88 percent in treating knee injuries involving cartilage

damage. It is used only for injuries, not arthritis. Genzyme Corporation of Cambridge, Massachusetts, licensed the technique from its Swedish inventor and is in the process of training 1,500 U.S. surgeons — including Rodrigo — to do the procedure.

Despite the high cost — \$30,000, which is more than the price for knee replacement or for D&M — Rodrigo sees the procedure as “a major step forward” that could ultimately replace D&M in certain patients. Currently, cartilage regrowth and replacement are offered only if other treatments fail. But Rodrigo is involved in studies to see if it could become the treatment of choice.

Despite 10 years of promising data, the Genzyme procedure remains controversial. Physicians at the last Academy meeting wondered whether cell reimplantation would survive the test of time. They wanted to see more evidence from controlled studies demonstrating the procedure's usefulness. The Academy itself stated that the technique remains unproven and long-term results are unknown.

Still, Rodrigo is optimistic that the procedure will find its place among the treatments UC Davis

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Cartilage transplants remain a focus of research

Ever since 1915, cartilage transplantation has been a tantalizing — and ultimately elusive — goal.

“Success rates have improved steadily,” said orthopaedic surgeon Juan J. Rodrigo, “but the ability to take cartilage from a recently deceased young person and transplant it into a recipient — usually a trauma victim — is far from a standard procedure. The current success rate is 75 percent to 80 percent; but surgeons like to see 90 percent.”

Rodrigo has performed more than 20 cartilage transplants since coming to UC Davis in 19XX. This is more than most of his colleagues at other universities. But the real promise of his program lies in his research lab. There, Rodrigo and his colleagues have been working on breaking down the barriers to routine transplantation and overcoming them one by one.

The initial hurdle facing cartilage transplant was simple: a lack of antibiotics, which kept the failure rate as high as 50 percent, primarily due to infection. After World War II, antibiotic drugs appeared as did a reliable tissue bank — courtesy of the U.S. Navy. Success rates shot up close to where they are now.

Since then, Rodrigo and his colleagues have been struggling with what may be the final barrier: an aggressive immune response. As happens when other organs are implanted, the recipient's immune system often puts up a spirited fight against the donated tissue, which it perceives as an “intruder.” In animal experiments, Rodrigo attempted to reduce this with immune-suppressant drugs. “They eliminated rejection, all right,” said Rodrigo. The problem was, they were also


toxic, sometimes fatally so. “You wouldn't want to do a knee joint implantation and then have your patients die from complications from a drug.”

So he began working on other methods. Suspecting that cartilage itself is not the perceived “intruder,” but rather the bits of bone tissue that cling to it, he began looking for ways to make the donated tissue “invisible” to the recipient's immune system.

Strangely enough, a cousin of ordinary household detergent may be the answer. Using a laboratory detergent called “Triton-X,” Rodrigo has succeeded at shrinking the immune response of the recipient animals. The detergent partially digests the bone cells and makes them seem less of a threat; detergent damage. “The cartilage cells are hidden to a certain extent,” he said.

It will take a good two years before human trials can begin. Before that, Rodrigo and his colleagues will have to make sure that any detergent that clings to the cartilage implants is not toxic to human patients. Furthermore, he will have to be careful that the implanted mixture of cartilage and partly digested bone cells retains its desirable properties, such as their ability to bond to the existing bone and cartilage. “Adding detergent might change the healing properties of the implant,” said Rodrigo. Just like toxic immune-suppressant drugs, “You might get rid of one problem and give yourself another.”

Rodrigo likens his cartilage transplant project to a quest for a magic elixir that will help him create the ideal transplant material.

“I've been looking for 25 years,” he adds with a laugh, “and I haven't found it yet.” 

About the source

Jan Paul Muizelaar earned his medical and doctorate degrees at the University of Amsterdam School of Medicine. In 1974 he completed a fellowship in neurophysiology at the Netherlands Central Institute of Brain Research. He completed his residency at the Military Hospital in Utrecht and the University of Nymegen and the University of Amsterdam. In 1982 he completed a fellowship in neurosurgery at the Medical College of Virginia in Richmond joining the staff as assistant professor of neurosurgery in 1982. He was appointed the Lind Lawrence Chair in 1987 becoming vice chair of the Division of Neurosurgery in 1991. Three years later he accepted an appointment as professor of neurosurgery and director of the Detroit Neurotrauma Institute at Wayne State University. He joined the faculty at UC Davis as department chair in May 1997. He can be reached at (916) 734-3658.

Neurosurgery chair specializes in treating traumatic brain injury

Jan Paul Muizelaar is infectiously enthusiastic. He speaks quickly and decisively about his plans for the Department of Neurological Surgery while sprinkling his conversation with a generous amount of easy-going humor.

A nationally recognized expert in vascular surgery, head injury and trauma, he was appointed professor and chair in May. He was attracted to UC Davis because the teaching hospital has such a high volume of trauma patients.

Muizelaar has already initiated important changes. The ICU is being equipped with special computers to monitor head injury patients and a new digital holography machine — one of only six in the nation — is on order to help surgeons image procedures before operating. To improve the residency training program, he plans to combine neurosurgery conferences with those at University of California, San Francisco and Stanford, thereby increasing the residents' exposure to cases and treatment plans and broadening their areas of discussion.

"Resident training is my first priority," Muizelaar said. "In many ways the combined conferences will serve as mock oral boards. For instance, UCSF's center would present their cases to

our residents who would then decide what kind of X-rays should be made. X-rays taken previously would be shown and the residents would have to explain what they see and then come up with a treatment plan and

an alternative plan. The process will help them think through cases in an organized fashion under the guidance of experienced people who will try to trip them up," he quipped.

Under Muizelaar's leadership, residents also will be exposed to a number of clinical trials. He is on the forefront of new treatments for stroke and head injury.

He is the principal investigator for an international phase III clinical trial of a pre-synaptic calcium channel blocker in severe head injury patients. The drug has shown promising preliminary results, appearing to protect against insufficient blood flow while normalizing metabolism in the injured brain.

"I am working on a paper showing that the neuropsychological outcome after severe head injury in rats is much improved with this drug," Muizelaar said. "Motor function, memory and learning capabilities are quite severely disturbed for 1 to 8 weeks after experimental head injury in rats. But this drug improves all of these problems considerably, and it is the only drug that can be given fairly late, up to 3 hours in rats, which equates to 20 hours after injury in humans."

Muizelaar is planning a multicenter, placebo-controlled clinical trial of the drug in comatose patients with severe trauma to determine whether CI1009 will improve outcomes.

He also is scientific advisor to a large, multicenter clinical trial of hypothermia in patients with severe head injuries. Led nationally by the University of Texas, Houston, UC Davis will be one of only seven research centers participating once the study criteria gets approved by the state senate.

"California law prohibits enrolling patients in clinical trials in which the body temperature is changed without informed con-



Vascular surgeon Jan Paul Muizelaar joins medical center as new chair.

sent," Muizelaar said. "But the law is contrary to federal law and those in other states. Hopefully, we can change it because many patients with head injury who are eligible for clinical trials are deeply comatose. Treatment needs to be started right away, and the family is not always available."

He has already sent a letter to Gov. Pete Wilson outlining his concerns.

Muizelaar's new plans for patient care include some of the most technically advanced equipment in the world.

A new holographic digital imaging device, which will convert CT or MRI scans, or even combine the two, into holographic images, will enable surgeons to see the injury and everything around it in space. "You can inject dye and see exactly where all of the blood vessels are in the head and whether there is an aneurysm in any of them," Muizelaar said.


"The device has special advantages for stroke patients because we can image blood vessels without doing angiography. Today strokes are being treated with clot busting drugs, but therapy must be admin-

"California law prohibits enrolling patients in clinical trials in which the body temperature is changed without informed consent. But the law is contrary to federal law and those in other states. Hopefully, we can change it because many patients with head injury who are eligible for clinical trials are deeply comatose. Treatment needs to be started right away, and the family is not always available."

istered within three hours to be effective. It would be ideal to know whether a patient has an occluded blood vessel before you give the medication because the drug has quite severe side effects."

In the ICU, Muizelaar is installing new computerized monitoring equipment to record all of the patient's physiological data, such as blood pressure, oxygenation of arterial blood, oxygenation of blood in the brain, cerebral blood flow and intracranial pressure. The monitoring system is so advanced that UC Davis will be one of only a few major centers in the world with this capability. Such systems are only available at the Medical College of Virginia, Wayne State University and Baylor College in the United States.

With so many new training, research and patient care efforts already under way, Muizelaar speaks rather modestly about his role.

"I feel UC Davis is a perfect fit for me," he said. "Here the emphasis is on trauma, and there is a real need for a vascular surgeon who performs acute neurosurgery." 

Connective tissue


(from page 9)

immigrants drifted into the computer business just out of college in the 1960s, according to a 1993 *Fortune* magazine profile. He was working at Amdahl when he struck out on his own with an idea for a software database that could enable big companies to manage corporate records on large mainframe computers.

Oracle, founded in 1977, soon catapulted Ellison to *Forbes* Magazine's list of America's 400 richest people. The company grew to become California's largest software firm and the third largest independent global supplier of database software. Today it employs more than 23,000 people in more than 100 countries and generates annual revenues of more

than \$4.2 billion.

With his \$5 million gift to UC Davis, the man behind Oracle is investing in a new vision: an Institute that will benefit patients with nerve, muscle and bone disorders for decades to come.

Said Chapman: "Thanks to this gift, we have the potential within 10 years of having a research program in musculoskeletal and neuromuscular biology here at Davis that will be unmatched. It will make available to the citizens of our region a level of care that is unparalleled and provide them with access to the most recent advances as they come along." 

Implantable pump delivers optimal dosages to quell chronic spasticity

Jennifer Bandalan's cheerful disposition seems incompatible with her painful muscle spasms and repetitive muscle contractions and relaxations. The 11-year-old is a reminder to her parents, doctors and therapists of cerebral palsy's cruel oppression.

There is no cure for cerebral palsy, which afflicts one of every 400 to 800 children born in this country. About 75 percent of the 750,000 U.S. residents with cerebral palsy suffer from chronic spasticity, which interferes with everything from standing to smiling.

Spasticity originates when areas of the brain or spinal cord that produce descending inhibitory impulses are damaged. Sensory signals from receptors escalate uncontrollably while stretch reflexes are deprived of normal negative modulation. Chronic spasticity contorts young bodies. It can

lead to musculoskeletal deformities. To relieve the symptoms, surgeons sometimes cut nerve fibers near the spinal cord that are involved in hyper-excitably reflex pathways. However, muscle flaccidity occasionally produced by such rhizotomies can be as debilitating as the spasticity they are intended to relieve.

Baclofen and other muscle relaxants blunt some of the symptoms. Baclofen, a structural analog of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), binds to GABA receptors, which are present primarily in the spinal cord and thalamus. The drug inhibits monosynaptic and polysynaptic excitatory transmissions, which thereby dampens uncontrolled reflexes. Unfortunately, baclofen doesn't diffuse into the area where it is needed the most — cerebrospinal fluid — so patients must be given large doses orally to try to increase cerebrospinal concentrations. The side effects can be sickening. Children often suffer nausea, headache and other side effects, and many also are too drowsy to read or listen attentively to a Dr. Seuss story.

In June 1996, Jennifer and hundreds other children with cerebral palsy in Craig McDonald's practice at UC Davis Medical Center could begin to dream of swinging on a swing, eating with a fork or sitting up on the sofa with a book. That was when the Food and Drug Administration approved intrathecal (within the spinal sheath) baclofen therapy to treat severe spasticity in children and adults with cerebral palsy, spinal cord injuries and multiple sclerosis. Jennifer and 6-year-old Vincent Gonzales were among the first of McDonald's patients to receive intrathecal baclofen therapy.

"Before, Vincent could stand on one leg," said his mother, Shawn Reynolds. The baclofen therapy relaxed his left leg enough so that Vincent could stand on both legs. "Now, he can walk," his mother said. "His dream is to run."

McDonald hopes Vincent's dream will come true. McDonald's intrathecal baclofen therapy program involves implanting a programmable infusion system, made by Medtronic Inc., of Minneapolis, Minnesota, under the abdominal skin of patients. The device continually pumps baclofen into patients' cerebrospinal fluid. (It can be programmed to increase the dosage at night to help patients sleep and lower the dosage during the day to improve muscle strength.) UC Davis neurosurgeon James Boggan has implanted the system in 20 of McDonald's patients, including Jennifer and Vincent. That's more than any medical center in the West.



Six-year old Vincent Gonzales can walk, but his dream is to run.

Prospective intrathecal baclofen therapy patients must meet age, weight and other patient-selection criteria. They also must show a significant reduction in their spasticity symptoms after they are given one injection of baclofen by lumbar puncture. While a small number of expected problems have cropped up with the baclofen pumps, the overall results have been stunning, McDonald said.

"The beauty of this treatment is we can bring these children in and do a single test dose with a bolus intrathecal injection and find out if the children respond without subjecting them to a surgery," McDonald said. The patients who receive the pump implants receive roughly one-100th of the daily oral dose of baclofen. "It certainly doesn't cure the cerebral palsy of patients who get the pump," he said, "but the functional results are pretty staggering at times."

In the surgery, Boggan inserts the tip of a silicone catheter into the fluid cavity of the anesthetized patient's spine and sutures it in place. He threads the remainder of the tube under the patient's skin, around their waist, to their abdominal area. Next, Boggan attaches the free end of the tube to the titanium implant device, a programmable infusion system. The device, about the size and shape of a hockey puck, contains a collapsible 10- or 18-milliliter reservoir with a refill port, lithium battery, peristaltic pump and antenna.

The FDA cleared the infusion system for intrathecal baclofen treatment of severe spasticity due to multiple sclerosis and spinal cord injury in 1992, and for intrathecal delivery of morphine for pain in 1991. More than 30,000 Medtronic pumps have been implanted worldwide, according to the company.

An integral part of the Medtronic pumps is an external device that looks like a laptop computer. Doctors use it to externally adjust the infusion rate of the pump with a radio telemetry signal. Within days of the operation, parents are dumfounded.

"I couldn't believe it," said Barbara Keeler, who with her husband Dave Keeler have been Jennifer's guardians since 10 days after the girl's birth. Jennifer, who previously couldn't sit up on a sofa, suddenly could sit up, unaided, on a bar stool and spin on it. She also could now draw a straight line with a pen and could easily transfer herself from her wheelchair to a chair or the toilet and into the seat of a swing in the back yard. Jennifer was functionally transformed.

"All I wanted to do was sit in my chair and watch her," said Barbara Keeler. "Even our care of her is 100 percent easier. Before, both of us had to hold her arms up to shave her underarms. Now, she holds her own arms up... Her voice is softer... Now, she is completely continent — we didn't even dream that would happen."

Parents like the Keelers predict that the baclofen pump will transform the lives and futures of other children as well. But there also are risks.

About 250 medical centers have installed Medtronic's baclofen pumps. Some of their patients have developed infections after the surgery, and in those cases surgeons removed the pumps. Also, the device's silicone tubes have kinked and pulled away from the spinal column in some cases, which requires a follow-up surgery to repair the problem. The pump must be replaced surgically every five years or so when the battery wears down.

Most patients and their parents willingly accept the risks. "For a while, people would tease Jennifer: 'Can I have your pump?'" said Keeler. "She'd say, 'No way.'"

McDonald currently is "titrating" Jennifer's baclofen dosage high enough to control her spasticity and low enough to avoid drowsiness and muscle weakness. Studies have shown that the intrathecal dosage of baclofen must be increased in most adults and children during the first year or two. Those studies have shown that only 5 percent of intrathecal baclofen patients become refractory to increased doses over time.

Because of the program's success, corrective orthopedic surgeries are no longer out of the question for McDonald's patients.

"Before intrathecal baclofen, the deformities would likely recur after the surgical procedures," he said. He recommended surgery for one of his patients, a 6-year-old girl with cerebral palsy, who couldn't stand because her spasticity had caused permanent leg and hip muscle contractures. "We've been able to control the spasticity with the baclofen pump, and she has had successful tendon-lengthening surgery to correct the deformities," he said. "She is standing in therapy now with braces on her legs."

Doctors and their patients' families interested in getting more information about Dr. Craig McDonald's Intrathecal Baclofen may call (916) 734-5293. [UCD](#)

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Ellison Chair

(from page 3)

in. By 1987, Genetics Institute and Creative Biomolecules had found the identity of the active substances, which most scientists started to call “bone morphogenic proteins.” Both companies have BMP-based compounds in clinical trials to repair and heal bone. With the help of his assay, the biotech companies “bottled the genie” of bone induction factor, said Reddi. But even though biotech companies took the prize, Rosen of Genetics Institute gives Reddi “enormous credit for having the patience and fortitude to stick with a purification project for 20 years.”

The experience of isolating bone induction factors gave Reddi unique insight into tissue formation. In some ways, bone is an unusual tissue but in other ways it is typical. Reddi began to formulate some general principles that have turned out to be pivotal for other tissues as well: Three elements are necessary for successful engineering of human tissues: inductive signals, like BMPs; responding cells; and the appropriate scaffolding or microenvironment.

These principles are just as useful in cartilage as they are in bone. Articular cartilage regeneration has been a difficult problem for science, Reddi is looking for ways to regenerate cartilage in patients who have had an injury or severe arthritis. “The structure where cartilage is replaced by bone is known as the

growth plate,” Reddi explained. At the growth plate, cartilage cells divide, then they die off and calcify, blood vessels come in and the cartilage is replaced by bone. “We’re asking what is responsible for the organization of the growth plate. I’d like to learn how this happens on a molecular level.”

But Reddi doesn’t want to stop at cartilage and bone. He is extending his work to ligaments as well, and like cartilage, no one knows how to regrow so that it is just like new. He is even looking at kidney regeneration, since kidney is a tissue that cannot be formed without the help of one of the BMPs. Scientists at Harvard University have shown that eliminating one of these BMPs in mice “completely knocks out kidney development,” he said. BioGen, another biotech company, has put over \$100 million into using BMP-7 to treat acute kidney disease.

“I want to let these factors lead me to other organ systems,” Reddi said, where he can apply principles he has learned so well from bone.

Ultimately Reddi’s work is leading him back to the study of the developing embryo, where most mysteries of the human body begin. “Cartilage begins to form in the embryo and is likely to be maintained throughout one’s lifetime by the same molecules. We need to isolate, maintain and purify these factors,” he said. [UCD](#)

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