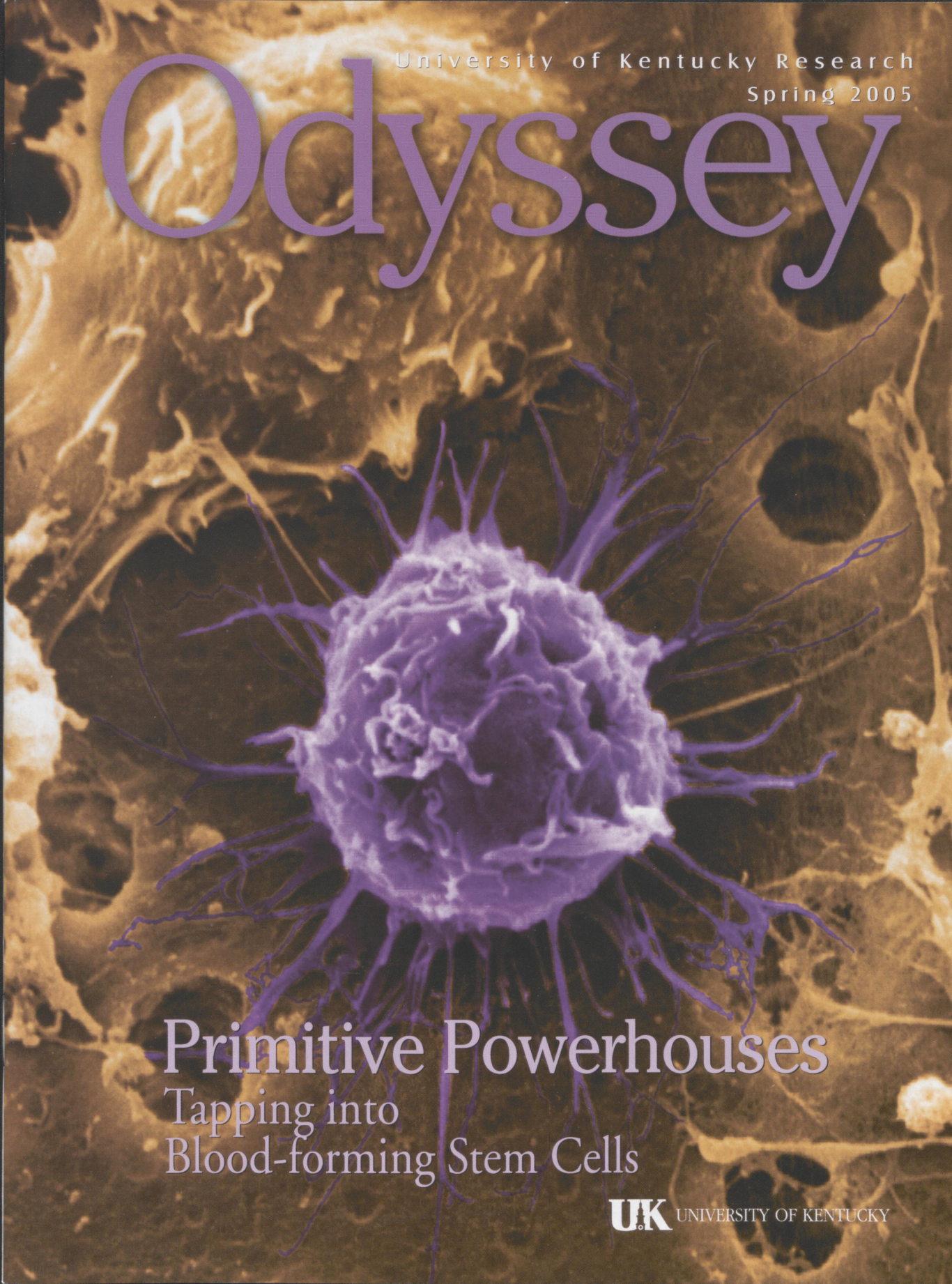


A microscopic image of a cell, likely a stem cell, with a central purple nucleus and numerous thin, branching purple filaments extending outwards. The background is a textured, golden-brown surface with some darker, circular features.

University of Kentucky Research

Spring 2005

Odyssey

Primitive Powerhouses
Tapping into
Blood-forming Stem Cells

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Cover image: This colorized scanning electron micrograph (SEM) shows a stem cell (purple) in human bone marrow. "The purple tendrils show important interactions between the stem cell and stromal cells that maintain the stem cell in its undifferentiated state," says Gary Van Zant. For more, see page 2.

Andrew Paul Leonard / Photo Researchers, Inc.

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Cover Story

Primitive Powerhouses: Tapping into Blood-forming Stem Cells

In his 10 years at UK, Gary Van Zant has probed the bone marrow's stem cells, and his findings have implications ranging from the immediate (better cancer treatment) to the seemingly sci-fi (organ regeneration). But what makes Van Zant's research unique among scientists investigating stem cells is his angle: aging. He's asking: What is the link between cancer and stem-cell aging?

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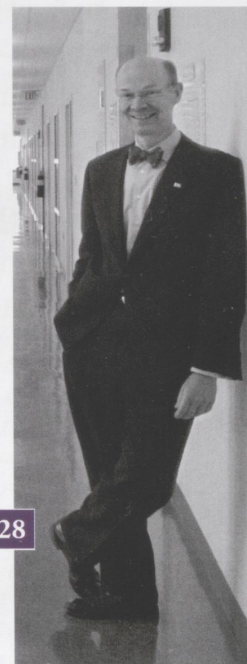
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The power to fight aging, knock out cancer, and regenerate tissue may have been hiding inside our bodies all along.

Scientists knew primitive powerhouses lived in our blood and bone marrow, but recent studies have uncovered them in organs never before thought to house them—the brain, heart and pancreas, to name just a few.

What are they? Stem cells: the self-renewing building blocks of the human body.

In his 10 years at the University of Kentucky, Gary Van Zant has probed the bone marrow's stem cells, and his findings have implications ranging from the immediate (better cancer treatment) to the seemingly sci-fi (organ regeneration). But what makes Van Zant's research unique among scientists investigating stem cells is his angle: aging.

He's looking at four main questions: What is the link between cancer and stem-cell aging, and what impact does that have on bone marrow transplantation? Does age play a role in a stem cell's ability to find its way home to the bone marrow after transplant? And what genes are involved in regulating stem-cell population size?

On Van Zant

Stem cell researcher Michael Clarke, a University of Michigan colleague of Van Zant in the mid-'90s, sums up Van Zant's research: "Gary has pioneered our understanding of the role that stem cells play in aging. He was the first to show that aging of an organ, specifically the bone marrow, was a consequence of loss of stem-cell function.

He then designed elegant genetic studies to identify specific genes that modulate stem-cell aging."

But before this "elegant" genetic research, in which Van Zant inserted human stem cells into genetically modified mice, his focus was blood. "I've always been interested in stem cells because they generate all of the cells in the circulating blood, and they have to do so for our entire lifespan because mature blood cells have very short lives," says Van Zant, who holds a Ph.D. in cell biology and hematology from New York University.

"Red blood cells live about 120 days, platelets [cells that cause blood to clot] live seven to 10 days, and granulocytes [a type of white blood cell] live only a few hours. Stem cells need to constantly replenish cells that are lost through regular wear and tear.

"So the question I began pondering was 'Do stem cells themselves wear out?'"

Not only has this question fueled his basic research, but the answer has immediate practical application to the clinical part of his job as director of the Stem Cell Processing Laboratory

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Tapping into Blood-forming Stem Cells

Written by Alicia P. Gregory

Primitive Powerhouses

"The natural course of aging and its undeniable association with cancer is not lost in a stem cell, despite its amazing ability to self-renew and restore tissue in times of need."

—Gary Van Zant



Gary Van Zant has spent a decade at UK studying age-related changes in bone marrow stem cells. Van Zant is a professor of internal medicine and physiology, and serves as director of the stem cell processing laboratory for the Markey Cancer Center Bone Marrow Transplant Program.

Stem Cells 101

"Stem cells are the ultimate resource for development, maintenance, regeneration, and repair in an organism," says Van Zant, but, he emphasizes, there's a clear distinction between embryonic stem cells and the "adult," fully developed, stem cells he uses in his research.

"The press and scientists have not done a good job in describing to the public the difference between embryonic stem cells and adult stem cells. Embryonic stem cells are controversial," he says, "and they are unique because they can grow into any kind of cell. They are necessary for fundamental research into understanding how stem cells are specified." But, he stresses, adult stem cells can yield their own important answers, and they're readily available.

"Adult stem cells are a resource that exists in all of us." His excitement builds as he explains that birth itself yields an "untouched reservoir" of stem cells. "We can get stem cells from the blood that exists at the time of birth in the placenta and in the umbilical cord of the fetus. And this resource is usually just discarded in the delivery room," says Van Zant. Stem cell treatment using blood from umbilical cords does not involve human embryos. For more on the value of umbilical cord stem cells, see page 9.

Adult stem cells have three general properties: they are capable of dividing and renewing themselves for long periods of time, they are unspecialized, and they give rise to specialized cell types.

A stem cell is unspecialized—it does not have any tissue-specific structures that allow it to perform specialized functions. A stem cell cannot carry oxygen through the bloodstream (like a red blood cell), and it cannot fire electrochemical signals to make the body speak or move (like a nerve cell). But stem cells spawn specialized cells like blood cells and nerve cells.

Unlike blood or nerve cells, which do not normally duplicate themselves, stem cells replicate many times over—a process called proliferation. They can create exact copies of themselves or they can breed specialized cells—a process called differentiation.

The triggers for cell differentiation are internal (signals from the cell's genes, which carry blueprints on how to build cell structures) and external (other cells in the immediate environment).

Inside our bones, Van Zant explains, stem cells have neighbors called stromal cells, which provide a sort of "pocket" for the stem cells. "Stromal cells provide a poorly understood series of biochemical and physical interactions that somehow keep stem cells from differentiating willy-nilly and prevent them from proliferating in an uncontrolled manner," he says, noting that uncontrolled cell division is the calling card of cancer.



Fifth-year graduate student Ying Liang and Gary Van Zant are pursuing a patent on a gene that she discovered which plays a key role in expanding stem cell numbers.

for UK's Markey Cancer Center Bone Marrow Transplant Program. He explains: "We harvest and freeze human stem cells that are going to be transplanted back into patients in the course of cancer treatment. To improve this process, the question I needed to answer was, 'Should we be concerned about how old the stem cells are that we're harvesting and transplanting?'"

Stem Cell Isolation

Blood-forming stem cells, known as hematopoietic stem cells (HSCs), have an identity problem.

First, they're rare. Scientists estimate that only one in every 10,000 to 15,000 bone marrow cells is an HSC. They live in the bone marrow—the soft, sponge-like material found inside bones—but they also circulate, at rates of one in 100,000 cells, in the bloodstream.

Second, you can't pick an HSC out of a line-up: they have no distinguishing features to separate them from look-alike blood and bone cells. Van Zant says, "This bedeviled hematopoietic researchers for a long, long time because HSCs are so rare, so nondescript, and have no markers of differentiation because they're primitive. It took many years before science could make stem cell purification routine."

The breakthrough came with a new technology: "Flow cytometry has been around since the 1950s, but it really took off with the development of monoclonal antibodies in the '70s," says Van Zant. Flow cytometry takes advantage of cell markers, specialized proteins on the surface of each cell—called receptors—that have the capability to adhere to other molecules. Cells use these receptors and the molecules that bind to them as a way to communicate with other cells and to carry out their proper function in the body. Monoclonal antibodies were developed for all kinds of cell markers, which allowed scientists to identify and separate different cell types.

The antibodies were coupled to fluorochromes—chemicals excited

by different wavelengths of laser light. "In an extremely rapid fashion, flow cytometry interrogates large numbers of cells on a cell-by-cell basis using laser beams," Van Zant explains. "Any lab studying hematopoiesis worth their salt has access to a very good flow cytometry facility. And we do here."

"Stem cells have certain markers that no other cells have, and, in addition, they don't have markers that most other cells do, so you can use this sort of yin and yang approach called negative/positive selection to isolate them."

He pulls out a chart of results from the last blood sample he ran through the flow cytometer. "Here, in a two-dimensional chart format, we've analyzed 50,000 cells in 40 seconds. You can take your bone marrow or blood sample into the flow cytometry room and walk out with a pure population of stem cells. Then you can study them in isolation from all of the other cells, and that ability has greatly advanced our work."

Age = Cancer

The biggest risk factor in cancer development is age, Van Zant points out, "and I'm talking about all kinds of cancer. Between the ages of 40 and 80, there is an exponential increase in cancer incidence. After age 80, it levels off."

"In cancers of the hematopoietic system, namely leukemias, the most studied is acute myeloid leukemia, or AML. AML is three times more likely to occur in someone age 65 versus someone 35."

Where does leukemia come from? Stem cells. "Studies have indicated that the original cell in AML was a primitive stem cell that took a wrong turn on the developmental pathway."

What happened?" he asks. "Most likely a buildup of mutations."

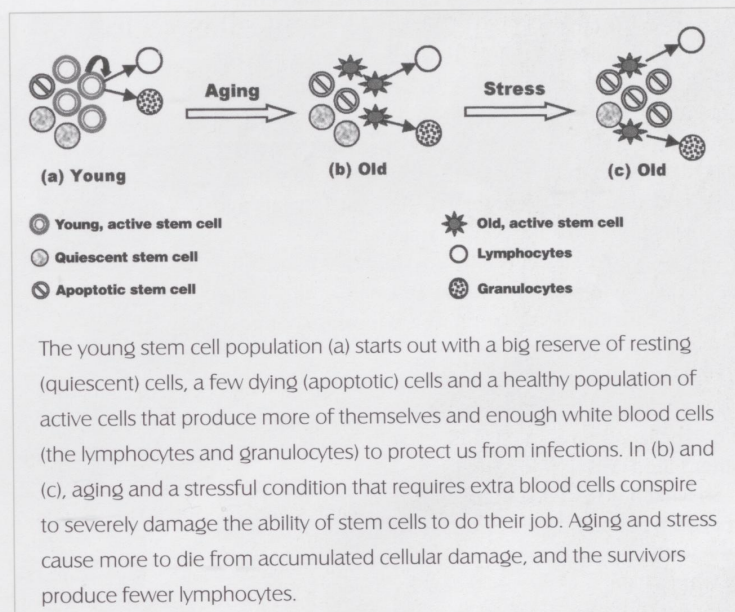
Van Zant's 10-person team, supported by a number of National Institutes of Health grants, is studying the age-related genetic changes that turn a normal cell into a cancerous one. "These genetic alterations can include independence in growth signaling, escape from apoptosis [cell death], and endless ability to replicate.

"A buildup of mutations takes place over the lifespan of an individual. And that buildup is due in part to repeated rounds of cell division that provide opportunities for editing errors in the DNA. That genetic damage is passed on to all of the stem cell's progeny. The inappropriate differentiation and proliferation of that damaged stem cell results in a tumor."

Van Zant says the failure of current cancer treatments just might be their inability to attack damaged stem cells. "Standard cancer treatments are aimed at end-stage cells, and they zero-in on them by exploiting the fact that end-stage cells divide rapidly." This rapid division causes the tumor to grow, but all the while the mother stem cell is relatively quiet. "She's not dividing much because she doesn't have to. Her progeny are doing the work.

"So it's a common theme: you treat the tumor with one of these drugs, and the tumor shrinks. It remains small for some time, but then it grows back. And a possible reason, at least in some cases, is that you haven't touched that 'quiescent' stem cell. It just takes that stem cell a little while to generate progeny again to grow the tumor."

The questions Van Zant is asking about stem cells apply not only to the link between cancer and aging.



The young stem cell population (a) starts out with a big reserve of resting (quiescent) cells, a few dying (apoptotic) cells and a healthy population of active cells that produce more of themselves and enough white blood cells (the lymphocytes and granulocytes) to protect us from infections. In (b) and (c), aging and a stressful condition that requires extra blood cells conspire to severely damage the ability of stem cells to do their job. Aging and stress cause more to die from accumulated cellular damage, and the survivors produce fewer lymphocytes.

"My over-arching philosophy is that the stem cells in various organs of the body could well be the focus for the age-related declines we see in those organs. Each organ suffers age-related decline in activity, but we haven't fully established what causes decline in a stem cell. Is it the ability to respond quickly to a signal that more mature cells need to be produced? Is it the inability of stem cells to divide in a rapid and appropriate way? We just don't know yet."

Stem Cells, Stem Cells Everywhere

The human body is filled with stem cells. "It used to be thought that stem cells were found in only a very few organs of the body—the bone marrow, the gut lining and the skin. This was the dogma for a long, long time," says Van Zant. "Recently—and this is

a huge area of research right now—numerous organs in the body are found to contain stem cells."

There are neural stem cells: "Of course the big push in that field is to find a way to repair central nervous system damage from accident or disease—Alzheimer's, Parkinson's. There are a number of childhood diseases that affect the central nervous system, and if you could go into the stem cells and repair the damage, it would have tremendous implications."

The pancreas has stem cells: "Diabetes is a huge problem in this country. Imagine if you could go in and fix the insulin-producing cells with stem cells."

Heart muscle contains stem cells: "It was thought that if you had an infarction—a great big chunk of your muscle was damaged—you were

continued on p. 8

Bone Marrow Transplant 101

Bone marrow is home to HSCs. "Hematopoietic tissue is nice because it's almost a liquid organ," says Van Zant. "You punch a hole in one end of the bone, stick a needle in the other end, squirt, and the whole plug of marrow comes out the other end. You can harvest and collect marrow very quickly."

But the process is painful. "In a bone marrow harvest, a patient goes to the OR, is anesthetized, punches are made across the back around the rim of the hipbone, and large amounts of marrow are pulled. It involves anesthesia—there's a certain risk there—and a recovery time," Van Zant says, but quickly points out that 10 years ago scientists found a better way to collect HSCs.

"We can inject a patient with a drug that causes the stem cells to leave the marrow and enter the circulation—we call this mobilization. This is the most common way of harvesting stem cells today."

The blood sample is passed through a machine (in a process called leukapheresis) that separates out the white blood cells, which contain the stem cells, and returns the other blood cells to the patient.

So what happens in a bone marrow transplant? There are two types: autologous transplants, in which patients receive their own stem cells; and allogeneic transplants, in which patients receive stem cells from a brother or sister or unrelated matched donor.

Van Zant sets up a hypothetical scenario for an autologous transplant. "You have cancer. You're early in your disease, so you're going to be responsive to drugs. We give you drugs, and you go into remission. We collect stem cells from your peripheral blood. We freeze those in liquid nitrogen down in the stem cell lab and put them away for later."

"We turn around and give you, essentially, a lethal dose of radiation or chemotherapy, and, we hope, this huge dose will kill all of your tumor cells, and maybe even some of the mutated, cancer-causing stem cells." He notes that this is the rationale for high-dose chemotherapy.

"You would die if we didn't have those bone marrow stem cells frozen. A day or two after your chemo, we inject into your blood a small number of stem cells. Those stem cells are going to have to replenish your entire hematopoietic system, and that's going to take some time. Meanwhile you're extremely vulnerable to infection, and the longer it takes for you to recover your white blood cell count, the more at risk you are from complications post-transplant."

"As a principal investigator, I have a tremendous responsibility to maintain funding for these projects because they support all of the people in my lab. I've got to look after my research family," says Gary Van Zant. Back row (left to right): Ying Liang, Adrienne Ellis, Jeff Yates, Barry Grimes, Carol Swiderski, and Amanda Waterstat. Front row: Mindi Haley, Debbie Bell, Erin Oakley, Van Zant, and Alison Miller.





Grad student Alison Miller (left) and postdoc Debbie Bell (center, background) have worked in Van Zant's research lab for two years. Grad student Amanda Waterstrat (right) has spent one year as part of a lab team that's been focusing on stem cell "homing" and population size.

pretty much out of luck. Now it's becoming apparent that quite a bit of regeneration occurs in the heart, and cardiac muscle stem cells apparently play a role in some degree of turnover."

Another exciting, albeit controversial, area of stem cell organ research is transdifferentiation, which Van Zant defines as "the ability of an adult stem cell to switch specificities to suit the environment in which it finds itself."

He sets up a transplant scenario: "Let's say you get a bone marrow transplant from a sibling. In half the cases that graft is going to be sex mismatched—because it's just as likely that your brother would be matched to you as your sister. So you, as a female, get a bone marrow transplant from your brother.

"In a real case, a woman got a bone marrow transplant from a man. Years after the transplant and after that

woman died, the doctor performing the autopsy wondered if the transplant had replenished any tissues other than the bone marrow. And low and behold, he looked in her heart and there were cardiac cells that were male. They could have only gotten there from the bone marrow cells that were transplanted into that woman. This is one of the strongest arguments for transdifferentiation."

Van Zant adds there's also evidence that scientists can take an adult stem cell from bone marrow, transplant it into a damaged liver, and replenish the liver cells. "There's also evidence that bone marrow stem cells can regenerate, or at least generate progeny, in the brain.

"But why doesn't this happen normally? Why don't the stem cells floating around in your blood 'get off the train' and migrate into damaged tissues? Well, there are obviously things

we don't understand, but the data's pretty tantalizing that, in fact, under some conditions, stem cells from the bone marrow can fix damage in other organs."

Mice as a Model

"If we measured the number of HSCs in the bone marrow of two 'normal' humans, like you and me, we may find that the difference is about 100-fold between us. And yet, we're both apparently normal. How can that be?" Van Zant asks, more animated with each word. "And what are the ramifications for the chances of one or the other of us getting leukemia or aging faster? These are the kinds of questions we hope to answer with mice.

"Mice mimic the vast majority of biological features that we find in humans, including aging. Only it's on a much accelerated chronological scale—in two years a mouse goes

through a series of processes that are mimicked in humans over eight or nine decades," he explains.

"In the bone marrow itself, the age-related changes in HSCs are very similar. In humans the bone marrow becomes hypocellular, that is, the number of cells in a given volume of bone marrow decreases with age. The same is true in the mouse. The nice thing about mice is you can get a group of mice that are genetically identical."

One such group, or "strain," of mice is immunodeficient (labeled by scientists as NOD/SCID—nonobese diabetic/severe combined immunodeficient). "This is a strain in which the immune system is completely wiped out. They have no immune response to anything. Scientists have used that mouse as a transplant model into which they've put human cells, and that's what we've done."

"You can give a mouse virtually the same treatments that are administered to a human in cancer therapy, and you can do a bone marrow transplant in a mouse that's virtually identical to one in a human. And the recovery patterns are very similar."

These similarities have allowed Van Zant's team to make two important discoveries.

"We've taken bone marrow stem cells from different age groups: people age 80 and older, middle age, adolescent, and newborns—from umbilical blood. We can study the differences in these stem cells very precisely by putting these cells into NOD/SCID mice. We can get actual numbers of stem cells, and see how quickly they repopulate the bone marrow."

Umbilical Cord Blood & UK's Cord Blood Bank

"Umbilical cord blood is a tremendous source of stem cells that's virtually untapped, because it's usually just thrown away in the delivery room," says Van Zant, who emphasizes that these are "adult," fully developed, stem cells.

"Go to any OB-GYN waiting room, and you'll see brochures for national commercial companies that will make sure your child's cord blood is harvested and stored indefinitely. Many parents are now getting savvy and paying to freeze their child's cord blood just in case the child develops leukemia or other diseases that can be treated with stem cells."

"At UK we're not in the business of storing blood for families," says Van Zant, who directs the year-and-a-half-old UK Cord Blood Bank. He adds that there are certain regulatory and liability issues to do so that the institution hasn't delved into. "We're interested in experimental and investigational use."

"So how do we obtain our blood? It's a partnership between the Cord Blood Bank and the people in OB-GYN, who get consent, as part of the regular paperwork mothers fill out, to donate their child's cord blood to research. A very large number of mothers agree to this."

"It takes a lot of cooperation from the OB-GYN residents who are actually in the delivery room, because, obviously, this is an afterthought to the big event," Van Zant says with a smile.

"At best you can get 50 to 100 milliliters of blood from the placenta and umbilical cord of a newborn. Although this blood is rich in stem cells, until recently it was simply not thought to contain enough

stem cells to transplant and repopulate the entire hematopoietic system of an adult. So it was used only in children who weighed 50 pounds or less."

But in December 2004, at the annual American Society for Hematology conference, two findings came out that may have a huge impact on umbilical cord blood transplantation.

"The first big finding, from a group at the University of Minnesota, was that it is feasible to pool cord blood from different—even completely unrelated—births to get enough stem cells for transplantation." Van Zant points out that scientists had been wary of combining sources because this could trigger undesirable immune responses. "The cord blood stem cells are very young, and they have diminished immune sensitivities, and it looks like you can, under some controlled conditions, combine them to get the numbers you need."

The second finding, the result of collaborative studies between Duke University, the University of Minnesota and the New York Blood Center, showed that perhaps the number of stem cells needed for an adult transplant is lower than scientists originally thought. Van Zant says, "They found that the number of stem cells actually needed, for most people, is within reach with the standard cord blood harvest. Now, that's only one study, and it needs to be followed up and duplicated, but it's very encouraging."

"Together these findings have really enhanced the possibility of expanding cord blood use for a wider number of transplants."

"We've learned two interesting things. First, old bone marrow doesn't repopulate the NOD/SCID mouse very well—not nearly as well as umbilical cord blood. And second, we have very convincing evidence that old stem cells have a greatly diminished capacity to find their way home to the bone marrow."

Scientists don't know a lot about stem cell "homing," and these are the questions Van Zant is tackling. "Is homing a random process? Is it just a scatter-gun approach—they go in, some of them hit the target, but 99.9 percent don't? Or can it be directed? Why do old stem cells find home less effectively than young stem cells?"

Van Zant says his findings so far are clinically important because they suggest that you may not want to bother harvesting stem cells from older donors. "Even if the stem cells themselves are 'good,' their age seems to automatically lower their chances of making it into the bone marrow."

Looking Forward

The very method of Van Zant's research means he can't predict where it's going to lead. He explains: "We know these mice are different in a very reproducible way, but what possible genes can cause that difference?"

The first step to identify genes is zeroing-in on the appropriate chromosomes. (Humans have approximately 30,000 genes on 23 pair of chromosomes—one of each pair you got from your mother, the other from your father. Mice have roughly the same number of genes on 20 pair of chromosomes.) "When you're looking at all possible genes, you never

"Umbilical cord blood is a tremendous source of stem cells that's virtually untapped, because it's usually just thrown away in the delivery room," says Gary Van Zant, who emphasizes that these are "adult," fully developed, stem cells.

know where you're going to end up. And that's exciting."

The most recent source of excitement is a genetic discovery by fifth-year graduate student Ying Liang, who works in Van Zant's lab. Van Zant cautions that he can't divulge too many details about this discovery because he and Liang are pursuing a patent on it, but he comments, "Her work makes us almost completely certain that this gene, that had never before been shown to have an effect on hematopoietic stem cells, appears to be very important."

Liang, a native of mainland China, says her work focuses on the regulation of stem cell numbers. "HSCs are very important in bone marrow transplantation. However, a big obstacle for this procedure [see sidebar on umbilical cord blood, previous page] is that inadequate numbers of stem cells are available for transplantation. Right now, we are looking for genes that might be responsible for expanding stem cell numbers, and we've already found a gene that may play such a role. I'm

testing the functions of this gene by overexpressing it [purposely producing excess] in HSCs to see whether or not the stem cell population increases."

Van Zant's team has located another target gene on Chromosome 11. "We have a very strong candidate, Rad50, a gene vital to DNA damage repair. This is important because the long-standing damage-response theory argues that aging is the result of accumulated damage to the macromolecules of cells—protein, lipids, nucleic acids—and that accumulated damage accounts for the physical manifestations we associate with age," he says.

Because stem cells are capable of spawning so many progeny, they must have "robust mechanisms of DNA repair. Defects in a critical DNA repair component such as Rad50 could seriously affect the ability of stem cells to function—particularly in old age," Van Zant says.

"If stem cells can't supply the appropriate numbers of progeny, aging is accelerated. And if DNA damage is not properly repaired by Rad50, mutations may result in tumor formation."

It all comes down to this: "The natural course of aging and its undeniable association with cancer is not lost in a stem cell, despite its amazing ability to self-renew and restore tissue in times of need. Stem cells have tremendous potential. And we're here to help answer the basic questions that will lead to a new generation of cellular therapies." ■

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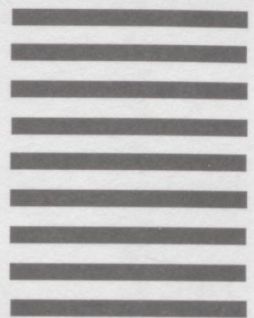
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Albert Einstein looms large atop a black bookcase in the office of Kozo Saito. In the poster-sized photo, Einstein's white hair is wild and tangled. His eyes are crinkled in merriment.

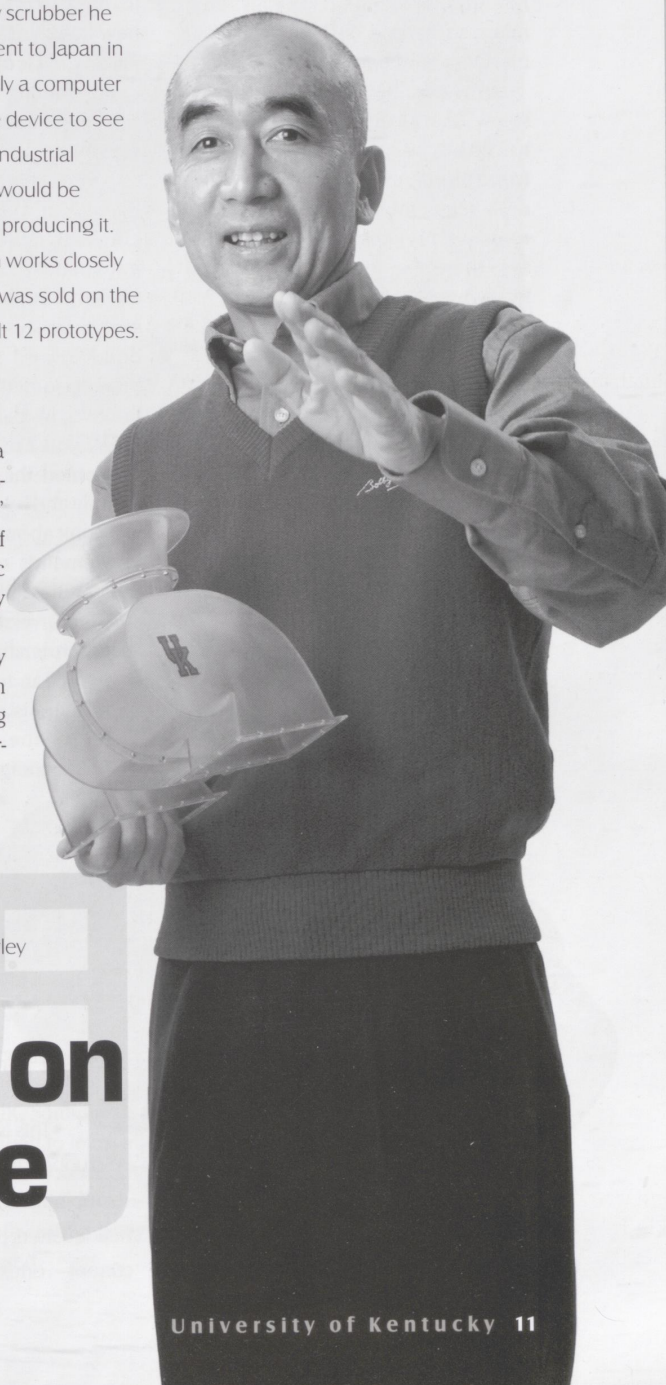
"Yes, he's a hero of mine," says Saito, whose easy smile makes you think of a boy who's just discovered a new Christmas bike under the tree, "but not so much for his mathematical theories. It's Einstein's *philosophy* that interests me more, his belief that science should serve human ends."

Saito, a professor of mechanical engineering at the University of Kentucky, readily admits he is a "philosophy-based engineer," a result, he says, of his Japanese heritage.

"I'm a big believer in the principles of *Genchi-Genba*, a manufacturing philosophy in Japan rooted in age-old craftsmanship. '*Genchi*' means, roughly, 'exact location'; '*Genba*' refers to function. The philosophy underlies the importance of interacting with things and problems directly, and in a specific context. It's a way to contextualize problem-solving in a very concrete way."

And for Saito, who began his work at UK in the late 1980s by tackling the problem of fire detection and spread (he even helped build and "nurture," he says, a robot capable of being guided remotely to fight fire), seemingly no branch of engineer-

Kozo Saito, seen here with a small plastic model of the revolutionary scrubber he designed, went to Japan in 1997 with only a computer sketch of the device to see if the Trinity Industrial Corporation would be interested in producing it. Trinity, which works closely with Toyota, was sold on the idea and built 12 prototypes.



Putting the Brakes on Paint Waste

Written by Jeff Worley
and Keith Elkins

ing is uninteresting. He specializes, at the moment, in combustion, fire research, painting technology, thermal sensing and control, and scale modeling and lean production.

In the past few years, this Renaissance Man of Engineering has narrowed his research focus, somewhat, to the problem of paint waste in automobile assembly plants and its environmental repercussions. And Saito says there's an interesting story that led him into this work.

パートナーシップ

Saito rolls the years back to New Year's Day, 1987. He was at a meeting in Lexington of the Japan Club of Central Kentucky, and he met a man who changed his life.

"You are Dr. Saito," the man said. "I am Fujio Cho."

Saito didn't recognize the name and exchanged pleasantries. He learned later that evening that his new acquaintance was president of Toyota's Georgetown, Kentucky, plant. Feeling that he had slighted Cho, Saito sought him out to apologize for not recognizing him.

Cho assured him he was not offended, and asked Saito about his current work at UK. Then Cho, clearly intrigued by Saito and his research background, floated out an idea: He said they should work together to build toward some kind of grand project, something that would allow the two, in a significant way, to say thank you to Kentucky, which had welcomed the Japanese natives so warmly and had given them so much.

"Think about it," Cho said, placing no demands or restrictions on the possibilities. "We'll start small."

This conversation led to an important partnership and, 10 years later, a solution to one of the automobile industry's most costly problems—the waste of electrical energy and paint during the coating process.

But we're jumping ahead of the story. First, there was the smaller project Cho alluded to, a trial balloon of sorts. This project focused on a problem Toyota was

having with transmission fluid levels in cars exported from Japan. Engine fluids are typically removed from cars before they leave Japan for the United States in order to lighten the shipping load; but inconsistency in the amount of transmission fluid drained resulted in varying amounts of fluid left in the cars. When the transmissions were given a standard amount of fluid in the United States, some cars would be overfilled, others underfilled.

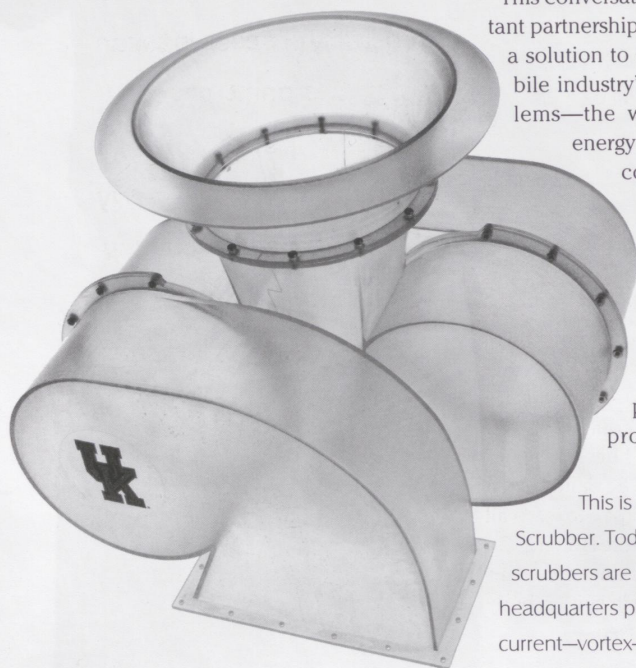
The goal was for each car to have the same volume, and to reach that goal Saito tapped into the engineering principles of volume and pressure.

With two engineering colleagues, he designed a pipe with a sensor attached to the end that could accurately detect, through the principle of "back pressure," the amount of liquid pressure released in the refilling process. In this way, just as a gas pump automatically shuts off when your tank is full, the sensor could register "full" no matter how much transmission fluid was initially present.

Was this a tough nut to crack?

"No," Saito chuckles, "it was really pretty easy. It was a small project. Mr. Cho just wanted to get a sense of how our group at UK would handle a problem like this."

A few months later, though, Cho, obviously pleased with Saito's first assignment, called him for some help on a much larger problem.



This is a plastic, one-eighth scale model of Saito's Vortecone Scrubber. Today, several dozen of these four-foot-tall, stainless steel scrubbers are used in seven Toyota facilities worldwide, including the headquarters plant. The device gets its name by combining the circular current—vortex—of water and paint with the scrubber's conelike shape.



Kozo Saito (second from right), director of UK's Painting Technology Consortium, inspects an automotive rotary-sprayer testing system used to validate the results of his group's computer models. From left to right: Abraham Salazar, assistant director of the consortium; Tianxiang Li, engineer associate senior; Kazunori Kuwana, engineer associate; and Fengguan Wang, a Ph.D. student in mechanical engineering. The goal of the consortium, established in 1999, is to help industries understand mechanisms of the painting process so that it can be done more efficiently, more cleanly and more cheaply.

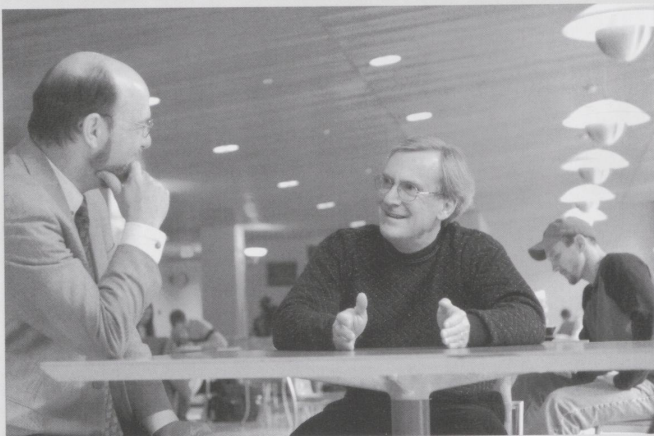
"Close to 50 percent of the energy consumption in the entire automobile assembly process is taken up by the paint process," Saito says. "Wasted paint due to overspray costs nearly \$1 billion a year, industry-wide, and of course environmental issues are an additional concern."

Saito, who had no experience with paint operations, toured Toyota's plant in Georgetown, with Naoji Tanaka, a vice president of the company, and saw firsthand the waste of paint as cars inched through the process. "You could see the paint particles in the air like a cloud of gnats, and you could see thick rivulets of paint run into the drains," Saito says. "It was clearly a huge problem."

Over the next two years, in addition to his regular work at UK, Saito visited over a dozen auto manufacturers around the country and in Japan to learn all he could about paint operations and the feeble overspray capture systems. On weekends, with production lines stopped in Georgetown, he changed from his street clothes into safety boots, thick gloves, and a "paint-booth suit," a body wrap of nylon overalls. Only the oval of Saito's face was exposed.

Close to 50 percent of the energy consumption in the entire automobile assembly process is taken up by the paint process. Wasted paint due to overspray costs nearly \$1 billion a year, industry-wide, and environmental issues are an additional concern.

UK and Industry: Partnering for Success



UK dean of the College of Engineering Tom Lester (left) talks with Toyota's Rich Alloo, who keeps an office in the UK Center for Manufacturing. At UK, Alloo monitors a variety of research activities to determine possible implications for improving productivity and quality at Toyota's plants in the United States and abroad. "This type of 'in-residence' relationship on a university campus is unique as far as I know," says Lester.

Eric Grulke, College of Engineering Associate Dean for Research and Graduate Studies, says, "Our research-for-development teams will infuse new technology into Kentucky's existing manufacturing industries, keeping them vital and competitive in today's global marketplace."

Faculty in UK's College of Engineering are working with the following companies:

- Akebono Brake Systems Engineering Center—Tingwen Wu
- Ashland Inc.—Eric Grulke
- The Asphalt Institute—Kamyar Mahboub
- Bussan Nanotech Research Institute—Kozo Saito & Eric Grulke
- CerWat Corporation—Rick Honaker
- Cypress Semiconductor—J. Robert Heath and Bruce Walcott
- Falkirk Mining Company—Rick Honaker
- Flashscan 3D—Larry Hassebrook
- Florida Institute of Phosphate Research—Dongping Tao
- General Electric Aircraft Engines—James McDonough
- General Motors Research—Fuqian Yang
- Honda—Kozo Saito
- Lexmark International—George Huang
- M2 Technologies Inc.—Daniel Lau
- NanoSonic Inc.—Robert Adams
- NextGen Aeronautics—Jamey Jacob
- Optical Dynamics Company—Eric Grulke
- Procter & Gamble Company—D. B. Bhattacharyya

"These painting platforms are wet and messy," says Saito, "and with the flashlight I carried to inspect the undersections, I looked a little like a coal miner," he laughs. Based on engineering precepts he had already considered, and the guiding principle of *Genchi-Genba*, Saito examined the scrubbers housed in the undersection that were used to suck up, much like a vacuum cleaner, the wasted paint. "For one thing, these scrubbers weren't very efficient in getting up the 'dust,' the tiny paint particles left over. And we discovered that the scrubbers operated at around 95 percent efficiency, which sounds good but isn't: typically, a plant wastes 150 gallons of paint a day." These devices also were using a huge amount of energy—up to 200 kilowatts per vehicle.

"I knew what was basically wrong," Saito says. "Now all I had to do was figure out how to design a better scrubber."

ペンキ

In thinking about how to solve this problem, Saito caught a break: he met UK Ph.D. student Abraham Salazar. Salazar was looking for a new direction in his research, and Saito knew that with Salazar's expertise in computational fluid dynamics, he might be the ideal research partner.

"I knew we needed a new scrubber model to test, but before we could even think about building something, we had to work through mathematical equations and computers simulations, and I didn't have that background," Saito says. So he and Salazar went to work, with Cho's blessing and around \$150,000 from Toyota.

A few months later, based on his equations and simulations, Salazar

came up with a computer-drawn design for a new and much more efficient scrubber. Saito and Salazar showed Yukio Tamara, a newly arrived vice president at Toyota in Erlanger, Kentucky, what they'd sketched and explained how it would work. Tamara was impressed. He contacted the former vice president, Tanaka, and suggested he invite Saito to come to Japan (where Tanaka had gone to become senior managing director of the Trinity Industrial Corporation) to give a presentation on the potential of a revolutionary scrubber.

Armed only with this design rolled up in his briefcase, Saito went to Japan in late 1997 to present his invention-to-be to Trinity. Tanaka and half a dozen engineers heard Saito's presentation and were sold on the idea; and Tanaka agreed to produce a prototype. "We had the support of Yasuo Tanigawa, Toyota headquarters' general manager, and his endorsement was essential, since Trinity works closely with Toyota," Saito explains.

"This was a major executive decision," Saito adds, recalling that he was "a little stunned" at the impact this computer-drawn model had on the group there. Trinity not only built a prototype—they built 12 of them, all different sizes to see if size made a difference in the scrubber's efficiency.

"Mr. Tanaka put a dedicated team on this. It took six months of more than full-time work and, I heard later, around \$2 million once all the testing had been done." And that's how the Vortecone Scrubber, a joint invention by UK and Toyota, was born, says Saito, adding that he has great respect for Tanaka, who took a "sizeable gamble" on a device that hadn't, literally, even gotten off the drawing board.

世界的

Today, several dozen of Saito's Vortecone Scrubbers, which look a bit like a four-foot-tall meat grinder, are used in seven Toyota facilities worldwide, including the headquarters plant. (The device gets its name by combining the circular current—vortex—of water and paint with the scrubber's conelike shape.)

This invention, which Saito patented through the UK intellectual property development office, has significantly improved overspray capture while using much less energy than conventional scrubbers. Paint capturing efficiency is 98.2 percent, up from the 95 percent that was typical of traditional scrubbers, and the 3.2 percent difference is a significant one, according to Saito. The energy savings are impressive by anyone's standards: the Vortecone uses nearly half the energy that's sapped by old-style scrubbers. And the Vortecone needs to be "maintained" far less often—it has to be disassembled, examined and cleaned only every 24 months, compared to every three to six months for traditional scrubbers.

発明

Saito's projects are continuing, and his working relationships have expanded into the international arena. He is now working with nine companies and 10 academic groups worldwide. During a weeklong trip to Japan last February, Saito visited three major companies—Admatechs Co. Limited, Toyota and Nissan—to discuss ongoing projects focused on advances in painting technology and future collaborations.

And Saito's trip was merely a prelude to bigger things to come for UK.

Last December, Kentucky Governor Ernie Fletcher announced Kentucky's participation in the 2005 World Expo in Aichi, Japan, the first world exposition in the 21st century. Fifteen million visitors are expected to attend the expo, which runs from March 25 to September 25. The United States is one of 125 participating countries. Kentucky was featured at the U.S. Pavilion the week of May 16 to 22, hosting Japanese business executives, international tour operators and others.

"The upcoming world expo is extremely important to the Japanese people, who value education and culture exchange highly," says Saito, a Japanese citizen. "Such an event is one of the most important activities in Japanese culture."

The University of Kentucky used the pavilion during Kentucky Week primarily as an opportunity to further Saito's partnerships in Japan. UK President Lee Todd and Executive Vice President for Research Wendy Baldwin hosted a luncheon meeting for companies Saito is currently working with such as the Nippon Steel Corporation, the Asahi Sunac Corporation, Kansai Paint, Sekimoto SE Engineering, and Mitsui Bussan. Eric Grulke, College of Engineering associate dean for research and graduate studies, led the group from the college, which includes Saito; Keng Hoo Chuah, a postdoc in Saito's research group; Kazunori Kuwana, a research staff member; and Salazar.

And for Saito, there's a pleasing personal connection involved in this event, since he'll again be crossing paths with Fujio Cho, now president of Toyota Motor Corporation. "In a way, my old friend and I have come full circle since meeting in Kentucky in 1987," Saito says. ■

Designing More Benign Bugs

Written By Jeff Worley

When, at exactly 2 a.m. on a warm spring night in 1997, Davy Jones finally got the lab results he'd been hoping for, he was so excited he phoned his wife and research partner, Grace, and woke her out of a deep sleep. Was she upset about this untimely awakening?

"No! I was ecstatic," Grace says. "I jumped out of bed and threw on a jacket and ran to the lab."

What they had detected was the elusive result of a receptor binding to something called juvenile hormone, a substance that controls insect development and metamorphosis. "Before I called Grace and shouted



'Eureka' into her ear, I repeated the experiment to make sure it worked. It did. It was an absolute rush." And when Grace joined him in the lab, they tried the experiment a third time. Again it worked, and they were able to celebrate this Eureka moment together.

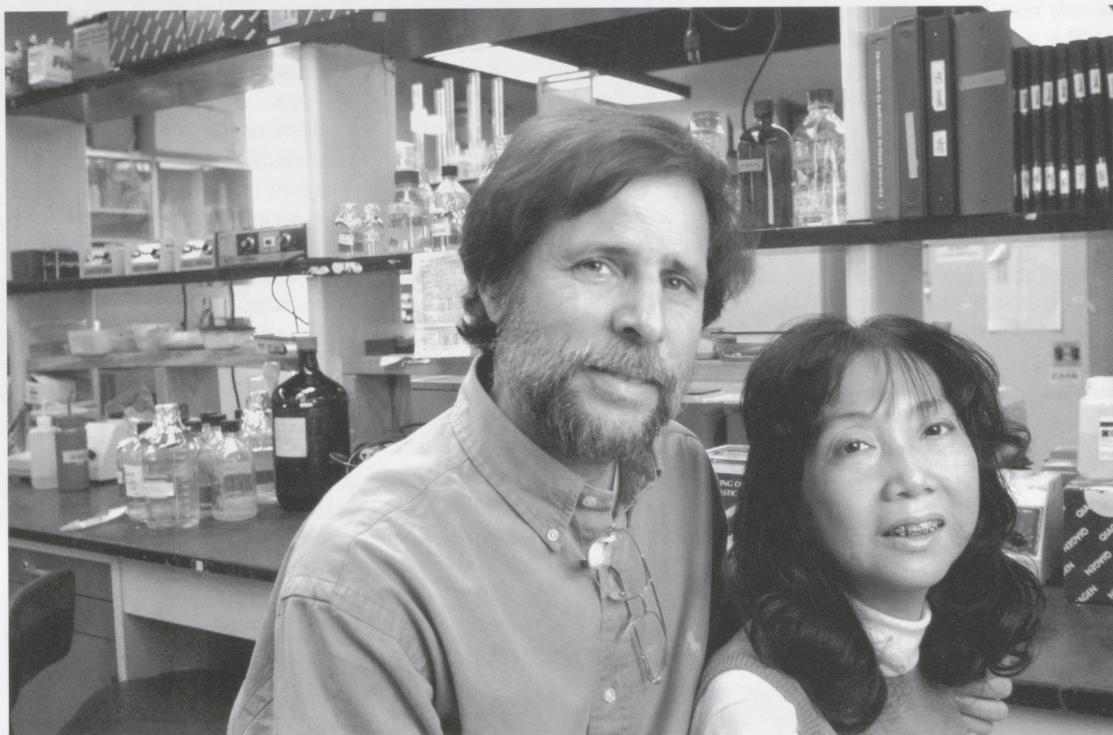
The two had been on sabbatical, working in exhausting 12-hour shifts at Rockefeller University in New York, where they chose to go, Davy says, because of the "environment of experts" there in gene biochemistry. The Joneses' goal was to find out how juvenile hormone binds, or doesn't

bind (chemically adhere), to specific receptors. At Rockefeller, the two continued experiments that Grace had recently begun at the Massachusetts Institute of Technology in the lab of Kentucky native and Nobel Prize-winner Phil Sharp.

Juvenile hormone gets its name from the fact that it causes the immature insect, such as the caterpillar, to remain in that stage instead of further developing to the adult stages—the moth or the butterfly. The goal of this work was to understand and be able to regulate insect growth.

As any gardener knows, a gang of caterpillars can eat vegetables right

Davy Jones, a professor of toxicology, and Grace Jones, a professor of biology, are working to control insect development.



UK research

duo

controlling

insect growth



down to the ground. Left to their own ravenous devices, the insects can eat all the leaves off large branches or small trees. "So we don't want the caterpillar to stay in this juvenile stage," says Grace. "We'd want it to develop as quickly as possible to adulthood and become a moth because moths don't eat plants."

Davy adds that with some other insects, the opposite growth pattern would be desirable. "We'd want the mosquito to stay in the juvenile stage and not advance to become the adult blood-sucker we dodge and swat."

The Joneses knew that insecticides based on their discovery could do either of these two things: accelerate or retard insect growth. "Rather than a broad spectrum pesticide, we wanted to find a selective 'magic bullet' that would stop the insect growth at the right stage but that wouldn't be toxic to humans and wildlife—something that wouldn't toxify the environment," Davy says.

Finding this magic bullet wasn't easy. A major challenge was to break through a scientific bottleneck in insect hormone research—to discover which protein receptors become activated when they interact with juvenile hormone. The physiological properties of juvenile hormone are well established, but finding the receptors that convert these properties had been like trying to fit a plug into an outlet in a pitch-black airplane hangar.

About six years ago, the research team decided to try a new technology that had not been utilized before in the insect hormone field, Davy

explains. They enlisted the aid of an amino acid component of proteins called tryptophan, which has the useful property of giving off fluorescent light when excited; but that fluorescence is disturbed if another chemical compound is bound nearby.

He and Grace identified a possible receptor they thought might bind juvenile hormone, and luckily this receptor

"Rather than a broad spectrum pesticide, we wanted to find a selective 'magic bullet' that would stop the insect growth at the right stage but that wouldn't be toxic to humans and wildlife—something that wouldn't toxify the environment."

—Davy Jones

has a naturally occurring tryptophan right next to where the hormone would bind. Tryptophan, they reasoned, could literally light the way to their hoped-for results.

"We envisioned that if juvenile hormone bound to this receptor, then we could detect that binding by its effect to disturb the fluorescence of the receptor," Davy says. "And this is exactly the case."

These results have generated two NIH grants and one NSF grant, a total of nearly \$2 million that has funded their

further exploration and refinement of this process. And UK has supported a patent application of the fluorescence technology.

As the Joneses worked to unravel the receptor mystery, they were confronted with a different, personal challenge. In August 2000, Grace suffered a severe stroke that left her body paralyzed on one side, severely limiting her mobility. In the foreseeable future Grace wouldn't be hustling back and forth between her lab and her husband's lab over at the medical center, which had for so long been her trademark style.

"It was great how at this point the department stepped up to help," Grace says. "Chuck Staben, our chairperson, went out of his way to make it possible for Davy to move his lab to the biology building, right across the hallway from me." Grace says her stroke has had one silver lining: it has brought home to her how important it is to understand how hormones stimulate the differentiation of cells into particular tissues. "A major limitation in the treatment of stroke or brain injury is a lack of understanding of how to stimulate regrowth of nerve tissue or how to direct stem cells to grow and replace injured nerve cells. If I can help the basic understanding of cellular differentiation in a way that eventually contributes to medical treatments that help other stroke sufferers 'metamorphose' back to their healthy state, that will be my most meaningful Eureka moment." ■

Remote-Control Surgery

Hi-Tech Robot Gives Surgeons a Hand

Written By Jeff Worley

UK's hospital was the first in the state to purchase and use the da Vinci system, which a surgeon controls from a console near the patient. Da Vinci allows surgeons to make smaller incisions, which reduce patients' pain, blood loss and recovery time. Four UK surgeons are currently using this system.

Intuitive Surgical

Star Wars surgery is now available in Kentucky. A four-armed robot, under the command of Stephen Strup, an associate professor of surgery at the University of Kentucky, successfully removed the cancerous prostate of Tony Curtsinger, 66, of Lexington. This robot is part of the \$1.3 million computer-assisted technology called the da Vinci Surgical System, which expands a surgeon's ability to operate within the human body in a less invasive way.

But wait a minute. You may have already seen this system in action. In the James Bond film "Die Another Day," which hit movie screens in 2002, the da Vinci Surgical System landed an unlikely supporting role. In one of the earliest scenes, at St. Mary's Hospital in London, the machine scans Bond's body and takes a blood sample, which turns out to be a vital action. Bond subsequently pursues questionable characters from Korea to London to Cuba.

Doctors at St. Mary's who use this system say da Vinci performed well in the role. And Sarah Robinson, product placement coordinator for the movie, echoed that view. "Both the producers and director thought this machine was fantastic. It's a very important part of the film."

"There's no reason now that you need to carry around an 8-inch scar like a war wound."

—Stephen Strup

The da Vinci system is, literally, cutting-edge technology, a tool for surgeons to do less invasive surgery, says Strup, who serves as the director of minimally invasive urological surgery in UK's College of Medicine. "When we can make smaller incisions, this significantly reduces the patient's pain, blood loss and recovery time."

Excizing a Cancerous Prostate

"When you can have an operation like this, go back to the doctor within a week, have the catheter taken out, and go back to work the same day, that's incredible and speaks for itself," says Tony Curtsinger, who owns a truck and trailer sales business in Lexington. "I was given pain medicine after the operation, but I never felt like I needed to take it." Now, over a year after the operation, Curtsinger says he has "absolutely no regrets" about choosing to be operated on by a robot.

"Dr. Strup was personable, open and honest, and it probably helped that I'm a mechanically minded person. I never had any fear." He adds that he talks freely with friends and acquaintances who are considering prostate surgery, sort of as an unofficial counselor. "I tell them the robot's the way to go."

According to the American Cancer Society, there will be about 233,000 new cases of prostate cancer in the United States in 2005. Over 30,000 men will die of this disease. Prostate cancer is the second leading cause of cancer death in men, behind only lung cancer.

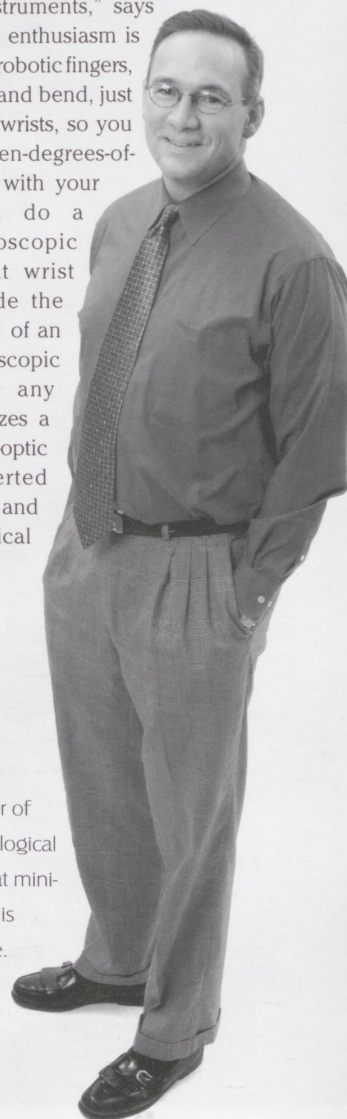
Prostate removal is the most common procedure performed on men with prostate cancer. The operation has been typically performed through large, open surgical incisions, which often result in lengthy and uncomfortable patient recovery. Not so with da Vinci. Using this system, surgeons make four or five, 1-centimeter incisions, through which an optical system and highly specialized instruments are slipped in. The optical system and the robotic arms are connected to a computer-driven mechanism controlled by a surgeon sitting at a console near the patient.

The surgeon looks through what appear to be binoculars inset in the console and views the magnified, three-dimensional surgical field. The operator then places the thumb and ring finger of each hand in plastic loops below the console. Specialized technology simultaneously transfers the surgeon's exact hand movements at the console to the extremely precise micro-surgical move-

ments of the robotic pincers ("hands") inside the patient's body. The surgeon can rotate the instruments 360 degrees through the incisions. The patient is under general anesthesia during the operation, which usually takes from two-and-a-half to four-and-a-half hours.

"The optical system provides high resolution and excellent depth perception. The picture is sharp and clear, and the tools allow you to do things that you can't do with straight instruments," says Strup, whose affable enthusiasm is infectious. "Using the robotic fingers, you can spin, rotate and bend, just like you move your wrists, so you have multiple, seven-degrees-of-freedom movement with your wrist. When you do a traditional laparoscopic operation, all that wrist movement is outside the patient on the end of an instrument." Laparoscopic surgery refers to any procedure that utilizes a laparoscope—a fiber-optic instrument inserted through an incision and used to guide surgical

Stephen Strup, director of minimally invasive urological surgery at UK, says that minimally invasive surgery is the wave of the future. "It's become more and more popular exactly because it's so patient-friendly."



Taking da Vinci to the Heart

Chand Ramaiah, an assistant professor in UK's cardiothoracic surgery division, recalls the exact moment he discovered his life's calling: his first day in medical school, when a cadaver convinced him to become a surgeon.

"This was in 1984, in an anatomy class at Bangalore Medical College in India. The professor held up a scalpel, gestured toward the cadaver, and said, 'Who wants to do some surgery?' Everybody kind of took a step back, so I took the knife from our professor and started in. I felt comfortable with this, and it was easy to project the good that could come from such work. I knew right then that doing surgery was how I could best help patients."

Ramaiah graduated from Bangalore five years later, then spent a year there as a rotating surgeon. After two more years of a residency at a New Delhi institute, he came to the United States and wound up at the University of Kentucky.

"During my residency in India, I met a young woman from Chicago. We wanted to get married and live in the U.S., so I started looking around for a place where my skills would fit, and a place we would like," says Ramaiah, an engaging, friendly man who also serves as director of minimally invasive cardiac surgery at UK. He came to Lexington in 1992 because a good friend of his was at UK.

His friend introduced him to someone in the Ph.D. program in neurosurgery who was looking for a postdoc scholar who knew some biochemistry, somebody who could "cleanly take rat brains," says Ramaiah, smiling at the obvious oddity of the phrase. So, armed with a background of nearly two years in neurosurgery, Ramaiah took the job. A short while later, he was accepted by the UK College of Medicine as a resident in general surgery.

His curriculum vitae now lists half a dozen "special



Chand Ramaiah specializes in off-pump bypass, esophageal, lung cancer, and cardiothoracic surgeries.

interests," including off-pump bypass, esophageal, lung cancer and cardiothoracic surgeries. And he's one of four surgeons at UK who use the da Vinci Surgical System.

Ramaiah agrees with Stephen Strup, director of minimally invasive urologic surgery at UK, that working with a robot has many important advantages: faster recovery time for patients, less loss of blood, a "magnificent view" of the operat-

ing field, and the advantage of making small incisions rather than long abdominal cross-cuts. This last plus is especially important in thoracic surgery.

"In traditional thoracic surgery you have to split the sternum—right in the middle—and then spread the rib cage to see the field of operation. With the robot, we can do the same operation with just three small cuts. Patients experience less back pain and side pain because we don't have to crank their chest open."

Ramaiah cites a couple of other advantages of working with the da Vinci robot. He's right-handed, and so favors his right hand when doing surgeries; however, when he's sitting at the console and directing da Vinci, he becomes ambidextrous. In addition, the robot's "hands," the pincers, are always steady—so there's no possibility of hand tremor.

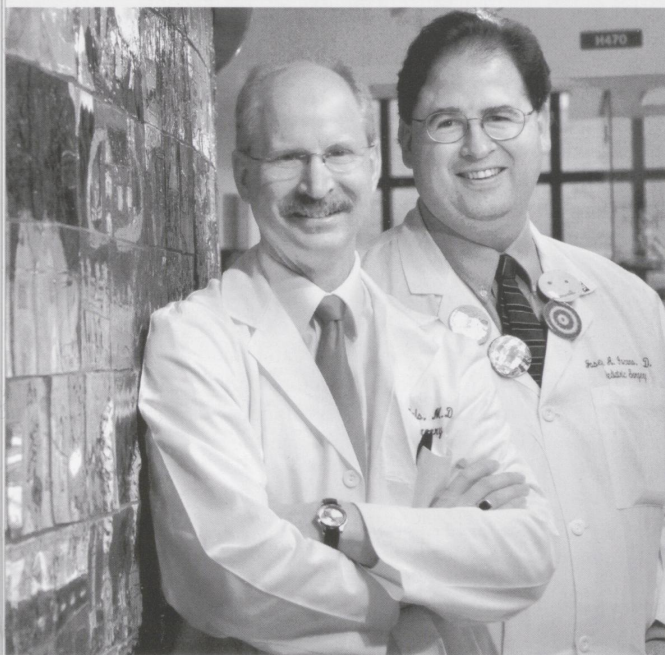
He does admit that robotic surgery has some downsides. The surgeon has no tactile feedback, he says, and there are some surgeries the system can't handle. Da Vinci can't be used for certain operations on the heart, like aortic valve replacement, and isn't practical to use to do heart transplants, since with transplants the chest has to be open anyway.

"But look at what it can do!" says Ramaiah, who has so far used the robot for 12 operations. "You'll be hearing a lot more about the da Vinci robot as time goes on."

procedures within the abdomen.

"The robotic system takes that movement and puts it a centimeter away from where you're working. This is one of the beauties of the system. When I'm working laparoscopically without the robot and using a straight instrument, if I need to go up 30 degrees into a corner, I have to move the whole instrument there. With the da Vinci system, I can just bend my wrist and grab and manipulate what I need to. I can work around corners. That's the advantage you gain."

Daniel Beals (left) and Joseph Iocono have teamed up to do four pediatric surgeries using the da Vinci system—three operations for gastroesophageal reflux disease and one thoracoscopy for removal of an esophageal duplication cyst. Beals is an associate professor in pediatrics and Iocono an assistant professor of surgery and pediatrics, and associate director of the Minimally Invasive Surgery Center at UK.



"There's enormous potential to take this onto hospital ships and into underserved areas all over the world, and ultimately that's where this technology will go."

—Stephen Strup

And this robotic system can be used for more than prostate surgery. More than 60 types of operations have been performed with the system, including abdominal, general thoracic, cardiac, and urological surgeries. Da Vinci has also been used to prepare internal mammary arteries for coronary bypass surgery and for operations on the stomach to stop severe heartburn.

"Minimally invasive surgery, which is what we're talking about with the da Vinci system, is the wave of the future. It's become more and more popular exactly because it's so patient-friendly, and that's why we're focusing our efforts on that here at the university," says Strup, who has done a dozen prostate operations so far at UK using the da Vinci. "There's no reason now that you need to carry around an 8-inch scar like a war wound."

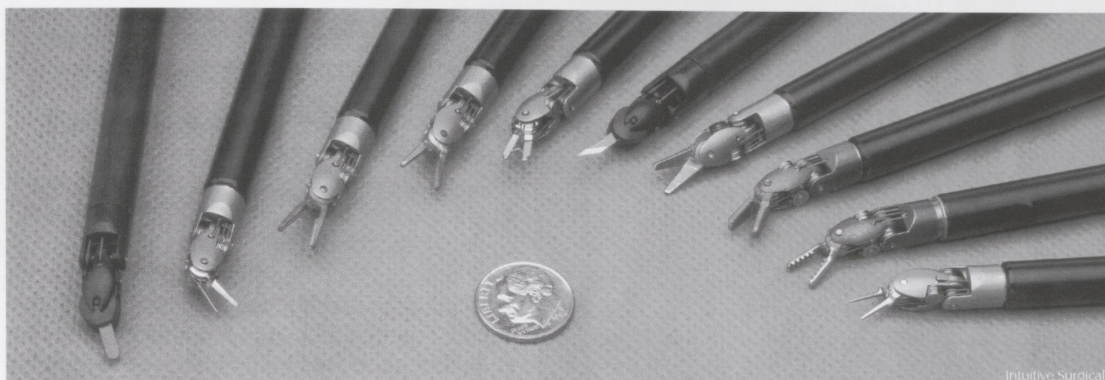
Making Friends with a Robot

Strup says the da Vinci system is fairly easy for surgeons to get the hang of, but admits he had some special challenges when he sat down to learn to operate it.

"Actually, of the group of us in 2003 who went for training in Nashville, where the da Vinci system is built, I probably had the most experience doing laparoscopic surgery—I probably had done 200 laparoscopic procedures by that time—and that put me at a *disadvantage* in learning the da Vinci system." Strup explains that before he could learn how to successfully operate da Vinci, he had to un-learn techniques and moves that had become second nature to him.

"As a surgeon, I've lived for the last 15 years in two dimensions. Along the way to being certified in laparoscopic surgery, I had to learn how to angle a needle and hold an instrument in a certain way to reach tiny areas, for example. But the da Vinci system is a three-dimensional world, so I had to adapt the vision of my mind."

Strup says that once a surgeon "gets it," though, and becomes comfortable working in 3-D, doing laparoscopic surgery is almost easy. "That's where I see this type of robotics going, because you can take a surgeon that has very little, if any, laparoscopic training and teach him in a short time how to do these surgeries."



He admits that although the da Vinci system might seem, to some, like something out of a science fiction novel, technology has a way of turning sci-fi into reality. "You could have said the same five years ago about cell phones or palm pilots. The da Vinci system is an amazing advancement, but, you know, it's already five or six years old. And with the advances in computing and engineering within the last few years, the next platform that comes out will be more refined, even smarter."

Strup digresses slightly to explain that the original idea of creating such a system dates back to the Vietnam War. The idea then was to build units that could be ushered into the battlefield so that wounded soldiers could be operated on almost where they fell. He paints an image of this system bolted to a cart and wheeled right up to the front lines. The idea of a surgeon rolling a robot onto the battlefield never materialized, but the concept lingered and was reincarnated as da Vinci.

So what is the future of this robotic system? Is it possible that surgeons will one day use it to do long-distance procedures?

"Oh, it's already been done," says Strup nonchalantly. "A year or so ago, using this system a surgeon in New York performed gall bladder surgery on a patient in Europe. There's enormous potential to take this onto hospital ships and into underserved areas all over the world, and ultimately that's where this technology will go."

You Can Go Home Again

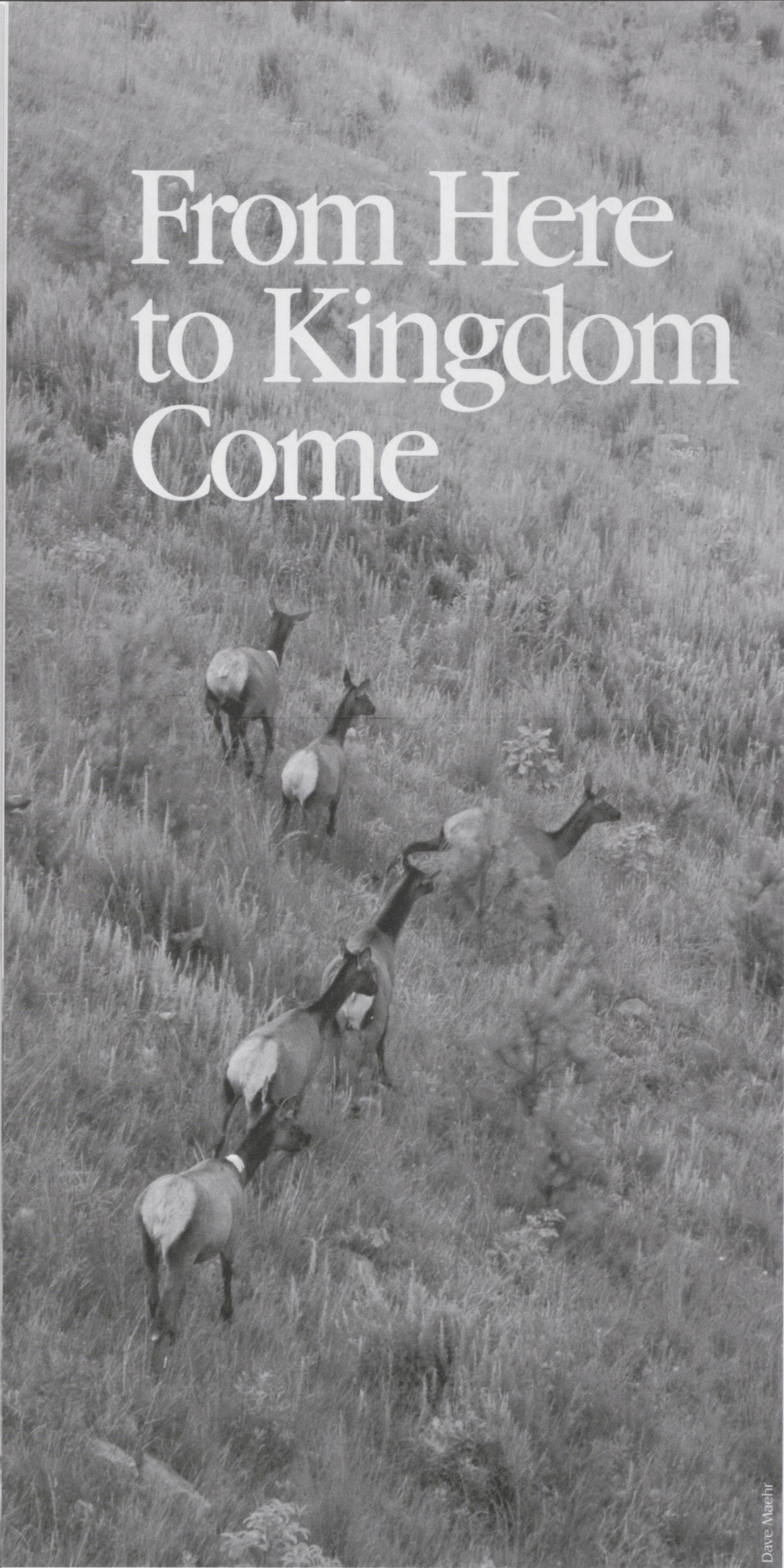
After earning his doctorate of medicine at the Indiana School of Medicine in 1988, Strup went to Thomas Jefferson University in Philadelphia, where he honed his skills in laparoscopic and laser surgery as an intern, and then as a resident. After his cancer fellowship at the National Cancer Institute, he returned to Philadelphia. A combination of things led him to UK in 2003.

The specialized technology of the da Vinci System transfers the surgeon's exact hand movements at the console to the extremely precise micro-surgical movements of the three robotic pincers ("hands") inside the patient's body. The surgeon can rotate the instruments 360 degrees through the incisions.

"The medical climate in Philadelphia is a really tough one right now. I had a huge practice, but the cost of doing business was just rising through the roof due to the total lack of malpractice control. I was paying roughly five times more there than what we pay here in Kentucky."

He adds that his 70-hour weeks completely eroded time for journal reading, writing and teaching, and, worse, severely cut into time with his family—his wife Sue and their children, Spencer and Sydney. These were all "push factors," Strup says, making it easier to think about going elsewhere; and Randall Rowland, chairman of the UK urology department, was a strong pull factor.

"In April 2002, Dr. Rowland invited me to come to UK to do grand rounds, and I did. I knew he was looking for somebody with a background in laparoscopic surgery, and I was thoroughly impressed with the quality of the residents. Also, Dr. Rowland and several hospital administrators said they would definitely consider purchasing the da Vinci system [which happened in January 2004]. So I went home and told my wife we ought to go to Lexington and have a look around." They did and they were sold. "My wife and I are from the Midwest [they met at a John Mellencamp concert], so it was a homecoming for us, really. Dr. Rowland is an outstanding leader and personality, and it was a nice opportunity for me to come into an area that didn't have a lot of minimally invasive surgery, a chance to make an impact." ■



From Here to Kingdom Come

**Wildlife biologist wants
bear and elk research
to reach wide audience**

Written By David Wheeler

Talking to Dave Maehr, you get the impression that he's always on the job. There was the time not too long ago, for example, when the wildlife biologist and UK associate professor of forestry was in bed recovering from hip surgery, taking strong pain medication. But he had also just begun a study on black bear recolonization in Eastern Kentucky and wanted updates from the field. Mike Orlando, a graduate student at the time, obliged. He took time to call Maehr in between tranquilizing bears and putting radio collars on them to track their movement.

"One morning around 7:30, the phone rang. I reached over in my drug-induced stupor, picked up the phone, and heard blow-by-blow details of the bears they had caught," Maehr says.

He sits back in his swivel chair and continues. "Mike was whispering, 'Now Dave, there's a big male bear, looks like about 400 pounds, walking down the hill right now. We've got the dart rifle ready; we're going to go in; we're going to shoot him. Wait ... wait ... quiet ...'"

Pop.

"There's a lot of rustling around, and then, 'We got him. Dave, I gotta go now.'"

Not long after that conversation, Maehr was back in the field.

He is not only dedicated to his work; he is also successful at it. Under his leadership, researchers are helping two species of large mammals flourish in a state where they had been extinct for more than a century. And according to Maehr, helping the animals means helping ourselves.

Dave Maehr

Maehr was one of 20 academic environmental scientists in the United States selected to be Aldo Leopold Fellows. Recipients are chosen based on scientific qualifications, leadership ability, and an interest in communicating environmental science to a wide audience.



A bear of a project

Black bears left Kentucky in the 1800s due to hunting and deforestation, but they began to resurface a few years ago in Kingdom Come State Park in Eastern Kentucky. They have now been sighted in at least 20 Kentucky counties.

Black bears nearly overrun Maehr's office—photographs of them, anyway. But Maehr doesn't need the photos to visualize them; when he talks about the bears, you can tell by the look in his eyes that he is picturing them perfectly.

"The bear recolonization happened under the radar," Maehr says. "It began with males that trickled into Kentucky. It took an occasional female to make it over and meet up with a male or two in the Pine Mountain area close to Cumberland, and actually start producing cubs, before the population started to take off. That happened seemingly without anyone knowing about it. We can't pinpoint a year where suddenly females were producing cubs and remaining in Kentucky their entire lives. It may have been anywhere from the early to late 1980s."

Maehr says the growing bear population is definitely a good thing. "What is so obvious to those of us who are in this field is that a healthy environment and all the attributes that go with it—the species, the processes, the competitive interactions that are out there—make for

stable, healthy ecosystems. Those are very important to us, because that's where we came from. We evolved as a species in competition with lions and bears and hyenas and diseases and parasites. But I think technology has really separated us from that, and as a result of that separation we have allowed ourselves to become so much less appreciative of the environment that we easily degrade it. And that's problematic for our future as a species."

For conservationists, the bears' return is a positive development, indicating that Kentuckians have made their forests hospitable to the animals again. For tourists, the bears are an exciting reason to visit the Cumberland area.

Others, however, fear that bears pose a danger to residents. A June 2004 article in the Louisville *Courier-Journal* sums up the tension with its headline, "The bears are back: Animals are an attraction, but can pose problems, too." "Just as bears can potentially hurt humans, the opposite is also true: Humans can hurt the bear population, out of fear or ignorance," says Maehr. Keeping both the bears and the people happy and safe is where his research comes in.

"Some people who live in areas where bears roam fear the animals because these people think bears will get

"No matter what one's politics are, everyone should agree on protecting the environment.

The environment should be the most non-partisan, 'apple-pie and motherhood' type of issue that we have in this country."

—Dave Maehr

into their garbage, scare their kids, or cause other kinds of damage. While this does happen occasionally, I think these fears are largely overblown."

Such a problem illuminates the scientist's true task, Maehr says. "I think that our ultimate challenge here is not so much to write papers and go to conferences, but to actually make conservation actions work on the ground."

Maehr launched a formal study of the bear population in 2002 with funding from the Kentucky Department of Fish and Wildlife. By putting radio collars on the bears, Maehr and his team are determining the size of the bear population, the area of their habitat, and the landscape features they seek out.

One of Maehr's first findings was that, contrary to the perception of some residents, the bear population was not in the hundreds. "Within a week of capturing these first few animals, we started recapturing them. And it became increasingly clear that just a handful of animals was being seen in a lot of different places, giving the impression that there were a lot of bears." Over time, Maehr will be able to develop a more accurate estimate of the black bear population. For now, he hesitates to give a number.

In the future, Maehr hopes to acquire funding for Global Positioning System (GPS) technology for the bear study. He has already used such technology to study bears in Florida, and he is currently using it to study elk in Kentucky. GPS collars provide detailed profiles of movement, revealing how animals cross highways, move around human habitations, and negotiate topographical features like rivers, mountain peaks and mining areas.

"The kind of data we can get from these collars will be anywhere from two or three locations a day to as many as one location every 15 minutes for an individual animal, and that kind of data can help develop some pretty intricate movement profiles," Maehr says.

Welcoming the elk

In December of 1997, Maehr stood on a hillside in Eastern Kentucky near Robinson Forest and watched elk return to a place they had not inhabited in 150 years.

"I remember it like it was yesterday," Maehr says,

"standing there on the hillside with 3,000 people who had been bused in from all over, watching the door open up from the trailer and seven elk running out. This very enthusiastic but subdued cheer went out, as if everyone knew if they made too much noise it would scare

the animals. They ran up a hillside together in a loose herd, stopped, turned back and looked at everybody, and then they just disappeared into the woods."

The event heralded not only the reintroduction of elk into Kentucky, but also an unprecedented research opportunity. As the principal investigator of the elk restoration project, Maehr organized a symposium and edited a book based on the project, *Large Mammal Restoration*. He says the large mammal work in Kentucky revolves around two questions: How capable is the landscape in supporting permanent populations, and what is the likelihood that these populations will continue to grow?

So far, the growth of the elk population has been impressive: now, an estimated 4,500 elk roam a 16-county area in Kentucky, thanks in part to elk brought in from other states. Because elk are usually the dominant species in a given area, some people were initially concerned that the animals might heft too much muscle and begin to reduce the deer population.

One of Maehr's graduate students studied this problem and came to a surprising conclusion. "The deer had a secret weapon in defending themselves against elk," says Maehr. "This is the brain worm—the more technical term is the meningeal worm—which is a native parasite in this part of the world. The brain worm doesn't affect deer; they're more or less immune. They've developed a resistance over hundreds of thousands or millions of years. But it's rather novel to elk, and it kills them."

Despite the parasite, the elk population is expected to reach 6,000 by summer 2005. Showing confidence in a stable elk population, the state issued 41 elk-hunting permits this year. Permission to hunt not only signifies a healthy population, but also reduces the likelihood that elk will damage crops and become a nuisance to farmers.

Hopes are high that the bear population will grow in a similar way. If the bear population shows stability, the state may one day issue bear-hunting licenses again. "The

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Black bears left Kentucky in the 1800s due to hunting and deforestation, but they began to resurface a few years ago in Kingdom Come State Park in Eastern Kentucky. By putting radio collars on the bears, Maehr and his team are determining the size of the bear population, the area of their habitat, and the landscape features they seek out.



best measure of successful management of the bear population will be when it, too, is able to be hunted—when Kentucky once again restores the tradition of bear hunting that preceded their disappearance back in the 1800s,” says Maehr.

Projects like the elk and bear studies are particularly important because large mammals require great amounts of space, draw public interest, and act as “conservation umbrellas,” Maehr says. In other words, success in protecting the large mammals in a particular area translates as success in protecting everything else in that forested system.

The environment, apple pie and motherhood

Whatever he’s studying, Maehr’s research has one central goal: to protect nature. “No matter what one’s politics are, everyone should agree on protecting the environment,” Maehr says. “The environment should be the most non-partisan, ‘apple-pie and motherhood’ type of issue that we have in this country.”

Through his research, Maehr wants people to realize that all the components of the natural landscape are essential to the survival of humanity. Though scientists

are sometimes unsuccessful in communicating their environmental vision beyond academic audiences, Maehr won a prestigious fellowship for his ability to reach the lay person: In March 2004, he was one of 20 academic environmental scientists in the United States selected to be Aldo Leopold Fellows. Recipients are chosen based on scientific qualifications, leadership ability, and an interest in communicating environmental science to a wide audience.

“Scientists are pretty good about communicating with each other, but when it comes time to influence policy, you’ve got to be able to deal with a legislator or an administrator, and make them understand the issues,” Maehr says. “You have to take a very straightforward and understandable approach.”

For a wildlife biologist like Maehr, understanding people is as important as understanding animals: “I learned that wildlife management is 90 percent people management, and that is certainly true. Everything that we do here, whether it’s on black bears or elk, is ultimately linked to people, and the values they have. Education is what it’s all about. We’re doing this work so that we can apply what we learn to improve our lives.” ■



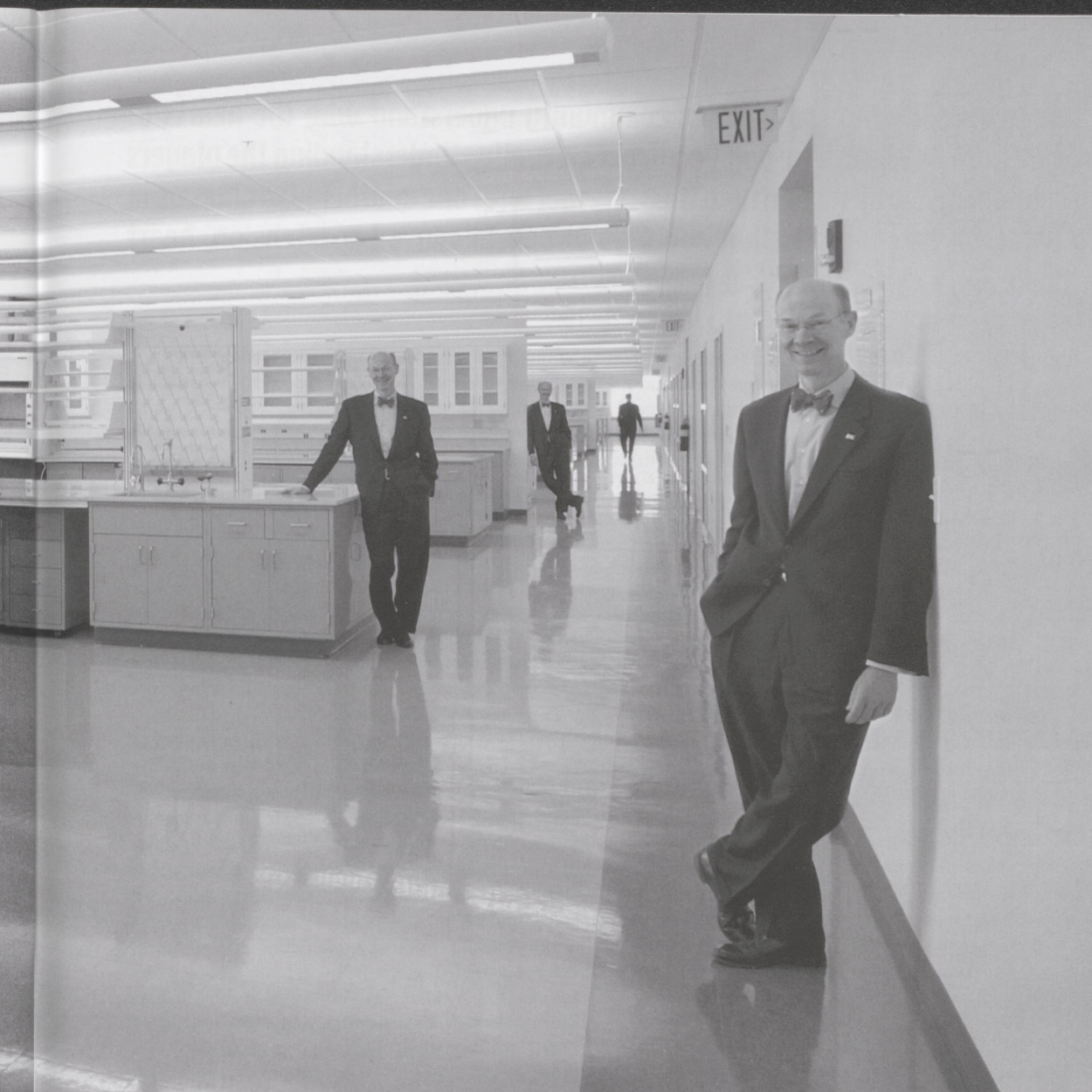
Room to Move

Top team of heart researchers comes to UK

Written By Jeff Worley

One of the reasons Jay Perman came to UK last year to become dean of the College of Medicine was UK's growing reputation as a top-notch research institution. But he wasn't so sold on the university's efforts to "grow," as he puts it, physician scientists.

"I saw a need for us to develop our clinical disciplines here so that more physicians could contribute to the national research agenda as physician-scientists. So I started thinking early on how we could



improve our efforts in the clinical area," says Perman, who also serves as the university's vice president for clinical affairs. He adds that this relative lack of growth in the clinical area isn't specific to UK; it's a shortcoming at other universities, too.

"There are plenty of reasons for the lack of physician-scientists. You need years of additional training for one thing. And there's the very understandable impulse among freshly minted physicians, after years of preparation, to get out there and serve humanity." He mentions, too, the simple lack of time physicians have to also train as scientists.

So Perman went looking for someone who could organize a wide-based clinical research effort here, and serendipity intervened.

"Last June I was part of an NIH group focused on preparing physicians to be scientists. Lo and behold, my recent University of Maryland colleague Bill Balke chaired this section." At Maryland, Balke had been chief of cardiology in the department of internal medicine and Perman chair of pediatrics.

In his lab space in UK's new \$74.4 million Biomedical Biological Sciences Research Building, William Balke is beside himself with anticipation as his team sets up shop to continue several projects that were under way at the University of Maryland. "It is amazing that so many people, mostly in early- to mid-career, have decided to come. It's really a testament to what's been built here and how those opportunities have been made obvious to potential faculty and staff who visit the College of Medicine."

"Our work can help the medical community understand why the hearts of people with heart disease don't contract normally. Understanding the players in calcium metabolism and how they interact with one another also clues us in to potential mechanisms that could go wrong to cause hypertension, heart attacks and heart failure."—William Balke

"I knew Bill was a national leader in developing programs for physicians who wanted to do research, and after a long day, we got together for old times' sake over a glass of wine. I told him I was looking for someone to head up clinical research at UK, and I encouraged him to apply when the position was announced."

Balke applied for the job, and after a lengthy search process the UK committee made him their top choice; so last fall Balke was offered the job and eagerly accepted.

Perman also knew that Balke's primary research focus, cardiovascular disease, couldn't have been more pertinent to Kentucky. "Along with his skills in developing clinical research programs, Bill brings an impressive background in heart research." Heart disease is the leading cause of death for Kentuckians. In 2001, Kentucky was ranked third in the nation for heart disease risk by the United Health Foundation. "Getting Bill here is a big plus for us in Kentucky."

The Maryland migration

This good news for the College of Medicine and for UK got even better in the weeks that followed. Balke was also bringing with him nearly his entire lab from the University of Maryland—faculty, postdocs and staff. When all the bags are unpacked and the dust from this influx of research talent has settled, as many as 20 new hires will set up shop in UK's new \$74.4 million Biomedical Biological Sciences Research Building.

Balke realizes that such a migration is unusual, but he emphasizes that he and his group weren't chomping at the bit to leave the University of Maryland. It was almost totally a "pull factor," says Balke, who manages to be soft-spoken and intense at the same time.

"It is amazing that so many people, mostly in early- to mid-career, have decided to come. It's really a testament to UK, to what's been built here and how those opportunities have been made obvious to potential faculty and staff who visit the College of Medicine."

Balke, sitting at a small round table in his office, one wall hidden by a fortress of unpacked boxes, says the primary reason he came was that he saw a career opportunity that would allow him to make a difference in how his work is translated into health benefits for people.

"What I see here is the possibility of coordinating various research projects in the colleges of Medicine,

Pharmacy, Nursing, Dentistry, Public Health, and other academic groups. This mutual reinforcement can really make a difference to the health and well-being of the population the university serves," says Balke, loosening his tie after a long day of introductory meetings.

What keeps calcium on the move?

Balke's lab will be running at full-speed by mid June, continuing half a dozen federally funded projects, to the tune of \$3 million to \$4 million, that focus on the underlying mechanics of the heart. This work builds on several successes the group has enjoyed recently.

The first project, focused on calcium release in cardiac cells, has gotten scientists a few steps closer to solving a longtime mystery.

"One of the important features of cardiac cells is their ability to take an electrical signal and turn it into mechanical movement so that a heartbeat initiates muscle contraction," Balke explains. "That's absolutely essential for blood to move through the body and nourish all the organs that it does. But exactly how the electrical impulse of the heartbeat causes the heart muscle to contract has been a mystery."

From previous work scientists knew that when the heart is stimulated with a heartbeat, the electricity excites changes in each heart cell, and that calcium goes inside the cell and becomes a trigger. What's triggered is the release of a much larger amount of calcium from inside the cell. That calcium activation causes the whole cell to shorten so that the heart muscle contracts and blood that's in the heart moves forward.

"Based on our own work and in partnerships with other scientists, we were able to use new technology, a laser scanning con-focal microscope, to visualize—in real time—calcium movements in a cell at a level that had never literally been seen before."

Using heart cells from rats, Balke's group added special indicators that glow when they bind to calcium, and because of the extremely high resolution of this microscope, the researchers could see the fluorescence. "With this tagging, we were able to describe in much greater detail the relationship between the calcium that enters the cell from the outside and the calcium that's released from the internal deposits in the cell."

Balke's team was able to determine the relationships of

dozens of molecules that serve as what he calls "micro-architecture" to move calcium from one place to another. The group then defined the key molecules involved in calcium triggering in a heart cell and the roles of these molecules. This description involved some very complicated math when the lab's results were published in *Science* magazine, but Balke says what they discovered can also be understood as a football analogy.

"We not only identified all the major players on the team, but we now know the roles expected of them. The moves of the quarterback, the fullback, the receivers—and how they handle their different positions."

Balke says the discovery is exciting in at least two ways. "It answers the most basic question of basic science—Why? And there are important potential applications for this discovery.

"Our work can help the medical community understand, at least partially, why the hearts of people with heart disease don't contract normally. Understanding the players in calcium metabolism and how they interact with one another also clues us in to potential mechanisms that could go wrong to cause hypertension, heart attacks and heart failure." He adds that his lab is using their discoveries about cell proteins and calcium in normal hearts as the basis for a new research focus: to try to understand and find solutions for hearts that go wrong.

"We hope down the line our work will impact patient care. You've heard that overworn expression 'bench to bedside?' I would borrow a page from *Lord of the Rings* and say that where we want to go is from 'bench to bedside and back again.'"

Doing some (ion) channel surfing

In a second major project, Balke and his team are working to characterize an ion channel they recently found on the surface of cardiac cells. He thinks this channel may play a role in arrhythmia (irregular heartbeats), and if this is true, their work has major implications for patients with this condition.

Think of cells as flashlight batteries. What makes the batteries work is the metal contacts they fit into. Like these metal contacts, ion channels in the cell allow electricity to pour through a cellular membrane so that the cell becomes activated.

"Almost through serendipity we discovered a new channel on the cell surface of most cardiac cells, and, coincidentally, it also happens to exist in most neurons. We don't know the function of this channel but suspect it plays a very important role in getting the cell to accept the electrical impulse of a heartbeat. If this is its role, then it may be a key player in potentially deadly arrhythmias."

His lab has been doing a rigorous study of this channel and what gene controls it, and this work will continue when the team re-groups here in June. Once the channel is understood, the lab plans to work with drug companies to identify pharmacologic agents that make the channel work better.

Balke is clearly excited by the potential of this work. "One outcome could be



Opening New Doors for Research

UK's newest building, the Biomedical Biological Sciences

Research Building (BBSRB), was dedicated on April 11,

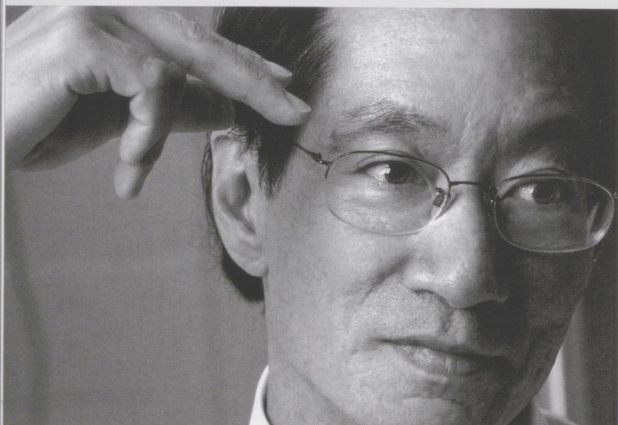
2005. The \$74.4 million research facility will house 400 faculty, staff and students focusing on neuroscience, proteomics and genomics.

In addition to Senior Associate Dean William Balke's Institute for Molecular Medicine, the BBSRB houses the Department of Molecular and Cellular

Biochemistry chaired by Louis Hersh, the Spinal Cord and Brain Injury Research Center directed by Edward Hall, and the College of Pharmacy's

Drug Abuse Treatment Research Program directed by Linda Dwoskin.

Leighton Izu: Understanding Arrhythmia by the Numbers



Leighton Izu, an assistant professor of medicine, is a member of William Balke's cardiovascular research group, which has come to UK in the past few months from the University of Maryland. Izu does complex mathematical formulas to determine how heart cells behave.

system can get off track. Specifically, he has been working to understand the

One of UK's most recent faculty hires is the first occupant of UK's newest building—the Biomedical Biological Sciences Research Building (BBSRB), west of the Kentucky Clinic across Limestone Street. Leighton Izu, an assistant professor of internal medicine, is one of several members of William Balke's cardiovascular research group who have come to UK in the past few months from the University of Maryland.

Back in February, Izu's second-floor office in the BBSRB was so new, it didn't have a number yet. Workers hammered all around him. The staccato bursts of a pneumatic drill rended the air. Two guys with electricians' belts pulled a huge red and black spaghetti of wires from the ceiling just outside his unpainted door.

"Yeah, I guess you could say I was a little eager to get started here," Izu says, gesturing toward the two tandemly linked, flat-screen computers on his desk, both screens pulsing with what appear to be complex mathematical formulas.

Izu's research focuses on understanding the system that controls calcium in heart cells and how that

link between the sudden change in behavior of the calcium control system and the onset of cardiac arrhythmias, or irregular heartbeats. Balke's group is studying the calcium control system by combining mathematical modeling and supercomputer simulations with more traditional lab experiments. The researchers work with rat heart cells, which, Izu says, are models for the heart cells of humans.

"Lately I've been working on what are called 'forward' problems: you have a model, in this case the heart cell, you focus on the most important parameters for the model, and then predict what the system is going to do given these parameters."

Izu says to think of parameters in terms of the performance of a car's engine. Just as an engine has many parts, the calcium control system has many components, each characterized by a set of parameters, such as calcium release units, transporters and channels. "A mechanic can tinker with many, many parameters and that will change the performance of your engine," says Izu, "and I'm doing the same thing with the cell's

calcium control system."

His work involves fine-tuning the performance of the heart to avoid arrhythmias. Izu explains that of the two types of arrhythmia—atrial and ventricular—atrial arrhythmias are the more common type and the least understood. The atria are the chambers of the heart that receive blood from the veins and force it into the ventricles.

"Lots of work has been done to try to understand ventricular arrhythmias, and that's totally understandable: If you have a ventricular arrhythmia, you have about a minute to live. You can live with an atrial arrhythmia for years. The fact that not much work has been done with atrial arrhythmia is a good scientific reason to study it—and mathematically, it's fascinating."

With his strong background in mathematics (a B.A. in math and a Ph.D. in biophysics), Izu assigns numerical values to the various parameters of the heart cell and then uses complex mathematical formulas to determine how, given these parameters, the cell will behave. He likens the interactions of the components of the calcium control system to the members of a jazz band.

"Each member adjusts his playing to the mood and tempo of the others, resulting in a dynamic and everchanging piece of music. A band of stubbornly independent members would produce nothing but noise. Likewise, if the control system components are uncoordinated, the calcium dynamics can be chaotic and could give rise to arrhythmias."

Izu laughs that with this analogy in mind, the whole concept of *conducting* research takes on an additional

meaning. "The point is, that using this mathematical modeling, I can predict and, I hope, control the outcome of the inner workings of a cell."

He admits that what he does is extremely complicated, which is why he works with experimentalists at UK and a major national laboratory to fine-tune his mathematical equations. He sends these equations describing the calcium control system to Sandia National Laboratories in Albuquerque, New Mexico.

In Albuquerque, Izu's colleagues turn these equations into dynamic 3-D representations of the cell's inner workings that, on his computer screen back in Lexington, pulse and flow. "You can actually see how the calcium release units set each other off, like a string of fireworks. You can see whether the flow of calcium is even or ragged; you can see which parts of the cell interact most strongly with their neighbors, and so forth."

Although Izu comes across as a man who would probably be happy no matter where he lived, he seems downright ebullient about being in Lexington. "I love it here. Being able to get from home to work and back is a whole lot easier and faster than in Baltimore." He's excited that so many of his lab partners at the University of Maryland have decided to come to UK, adding that he does have a "very favorite" lab partner—his wife Ye.

"Ye has very impressive mathematical abilities," Izu says, his tone an applause of sorts. "I'm horrible at doing routine math." He says that when he was working on his dissertation, he had terrible trouble simplifying some complicated equations. "Ye took a look at the equations and within an hour got the correct answer." [For Ye's narrative on her road to UK and her account of first meeting Leighton, go to www.research.uky.edu/odyssey/spring05/ye.html.]

Balke's group is studying the calcium control system by combining mathematical modeling and supercomputer simulations with more traditional lab experiments.

a pharmacologic alternative to implanting cardiac defibrillators in patients. Another implication might be that because this channel also exists on neurons, it may be a common feature of all cells that are excitable. If we discover that this channel is an important player in devastating neurological diseases, like epilepsy and Alzheimer's, this would be a major, major finding."

Toward better heart treatment

Balke says his group will continue to follow these two major projects where they lead and that several other projects related to cardiovascular disease will be launched at UK. "I hope the work on the ion channel is going to move us forward to understanding what's causing sudden cardiac death in patients and that we'll come up with a more effective way of treating that.

"And I think we're going to find a better environment here to do a systems-biology approach, in other words unite mathematics and molecular biology and physiology, and do multidisciplinary work in a way we couldn't when we were locked into the traditional silos of most academic medical centers," Balke adds.

He emphasizes that it's the unique combination of expertise in his research group that makes the unit so effective—and which allows the imagination of the whole group to blossom.

"We have physicians and we have Ph.D. scientists and technicians who are all equal citizens in the group. Several are experts in studying individual ion channels or molecules on the surface of the cell. Others are skilled in the imaging techniques we use to visualize calcium as it moves in the cell."

Balke singles out the crucial role played by the senior laboratory technician, Stacey McCulle. "She brings invaluable technical expertise to the group and has been absolutely essential in moving our lab forward over the last couple years."

"We're a tight-knit group, and I'm really glad to continue with Dr. Balke," says McCulle, who is planning to move to Lexington in June. "He doesn't micro-manage, and he fosters a good research environment."

Balke is also excited that the team's mathematician, Leighton Izu has come to UK. "Leighton contributes some amazing skills with mathematical modeling, a dimension of this research that few groups have."

"William Balke is a very major recruitment for us," says Perman. "To get somebody of Bill's caliber and national reputation to come—and move his lab here—is a major coup." ■

Good Bugs for Your Garden

They work 24/7 to police the pests that ravish our gardens and lawns. But too often gardeners or homeowners, thinking the only good bug is a dead bug, wipe them out with a few bursts of insecticide.

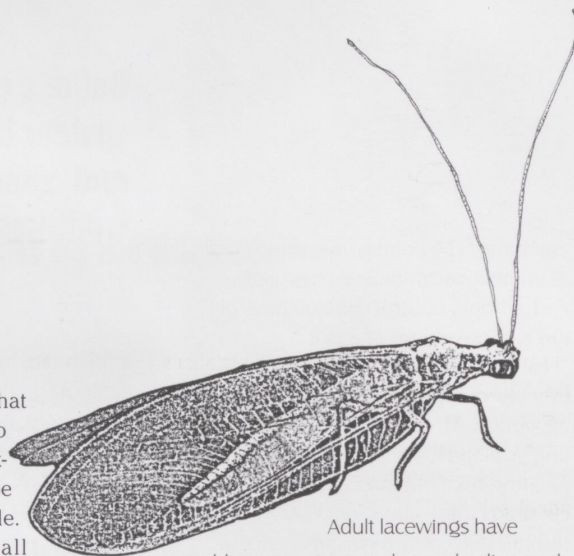
"There are some insects we call 'beneficials' because their behaviors help us control insects that otherwise like to eat our plants and gardens," says Ric Bessin, extension entomologist in UK's College of Agriculture who is working to educate gardeners. "Without beneficial insects, plants and flowers would be inundated with insect pests." Other beneficials also pollinate flowers, vegetables and crops, or help decompose organic matter in compost piles.

In Kentucky these good bugs include green lacewings, lady beetles, ground beetles, spiders, praying mantids, parasitic wasps, and bees, Bessin says. Lacewings are among the most important of these predators, he adds, because they feed on many soft-bodied insects such as aphids and mites.

It only takes a bit of work to be able to identify these good bugs. "We have a web site (www.ca.uky.edu/agripedia/agmania/insectid) where you can do this, and we have 250 fact sheets on various insects—many of those beneficials," Bessin says. Another good source of information is UK's county extension office (there's one in each of the state's 120 counties), which provides free insect identification.

"If gardeners want to take full advantage of the natural enemies in their garden, they really need to be careful in terms of what pesticides they use," says Bessin, who also teaches a class for people who aspire to be master gardeners. "Many new pesticides are selective and so don't impact the natural enemies as much." Again he recommends that gardeners contact their local extension office for publications that list the common pests in the area and that recommend appropriate pesticides.

"One way to ensure a better garden is simply to identify before you spray. Good bugs are our allies."



Adult lacewings have golden eyes, green or brown bodies, and are about three-fourths of an inch long. Lacewings are among the most important yard-and-garden predators because they feed on many soft-bodied insects such as aphids and mites.

UK's Asia Center Benefits Students

Bringing the University of Kentucky closer to Asia is the goal of the Asia Center, housed in Bradley Hall. The center, which began in January 2002 with start-up funds from the Freeman Foundation in Vermont, offers a yearly symposium on an Asian topic, a monthly colloquia, workshops for K-12 teachers, and an annual summer study tour to Asia, most recently to China. One result of all of these activities, says center director Kristin Stapleton, an associate professor of history at UK, is that students benefit.

"I attended the National Consortium on Teaching about Asia, and clearly my students have profitted," says Michelle Peck Williams, who teaches at Dunbar High School in Lexington. "In my world history classes, for example, one unit is 1914-present, and Asia plays a major role in that period. After attending the consortium, I have a lot stronger background in Asian history and politics." Williams teaches three humanities classes and three advance-placement world history classes, with a total of about 150 students.

"After last summer's trip, I was able to incorporate a unit titled 'Sociology of Agri-Food Systems' into my UK graduate seminar on China, which focuses on the country as a new global food power," says Larry Burmeister, an associ-

Written By Jeff Worley

ate professor of sociology who specializes in East Asian agriculture. "In my international human rights course, I now have my students work on issues concerning Chinese labor conditions," says Karen Mingst, a professor of political science at UK who also went on last summer's study tour.

UK students also benefit from a recent hire made through the Asia Center—Han Kuo-Huang, a specialist in East Asian and southeast Asian music. "I teach two classes—'Introduction to World Music (Asia and the Pacific),' with an enrollment of 40, and 'Gamelan,' which 10 students have signed up for," says Kuo-Huang, a professor of music at Northern Illinois University for over 30 years. A gamelan is an Indonesian orchestra made up essentially of percussion instruments.

"We're lucky to have someone of Kuo-Huang's caliber here," says Stapleton. "After we saw how well he worked with the teachers, and how much knowledge and enthusiasm he brought to one of our summer workshops, the Asia Center steering committee members all agreed we should see if he was interested in teaching here."

For more, visit www.uky.edu/Centers/Asia.

Toward a More Family-Friendly Workplace

All large companies have investment strategies, but Jennifer Swanberg, an assistant professor of social work at the University of Kentucky, believes too many businesses fail to invest in their most important asset: their workers.

In a recent report she co-authored, titled "Increasing the Visibility of the Invisible Workforce," she chronicles the impact of companies with innovative programs that benefit and retain hourly and low-wage employees.

"Too often there is a mismatch between the needs of working families and the needs of employers," says Swanberg, who came to UK in 2000. "The goal of our project was to find companies that have instituted new and innovative workplace practices for hourly workers. We were particularly interested in workplace strategies that assist employees in meeting their work, family and personal responsibilities. "The project was funded by Fleet Bank & Corporate Voices.

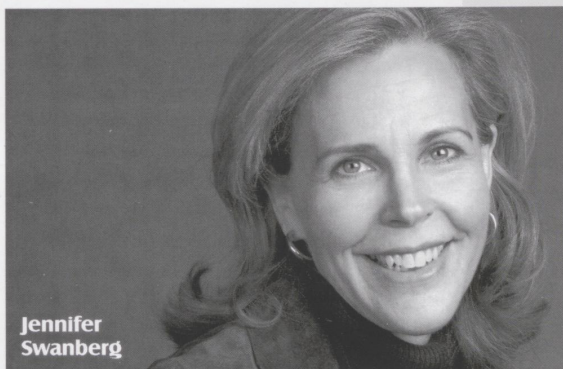
Swanberg and her colleague Leon Litchfield, the former director of research at the Center for Work & Family at Boston College, interviewed managers and employees at 15 organizations, including CVS/Pharmacy, Eddie Bauer, Home Depot, Kraft Foods, and Marriott International, which have subsidiaries in Kentucky. These companies have adopted a number of policies that have resulted in not only happier workers but also increased productivity.

For example, Kraft Foods instituted the "Fast Adapts" program in 2002, an initiative that has created a variety of flexible work arrangements for hourly employees and production supervisors who work in round-the-clock manufacturing facilities. Kraft developed the initiative in response to employee survey findings that hourly workers were not able to use the traditional flexible work arrangements offered by the company.

"The new policy, which allows hourly employees to switch shifts, gives employees the flexibility to attend to family or personal matters without having to use vacation or sick leave time," Swanberg explains. "Anecdotal evidence suggests that this flexibility has led to higher retention and more dedicated workers."

Bank of America offers a program that reimburses employees for the cost of child care. Monthly reimbursement amounts range according to the age of the child and type of care. Levi-Strauss & Co. established the Red Tab Foundation, which provides company employees and retirees grants and loans for unexpected financial hardships.

"The intent of this report, which was targeted for a business audience, was to highlight best practices as a way to demonstrate that there are a variety of workplace strategies that can be employed to assist hourly workers."

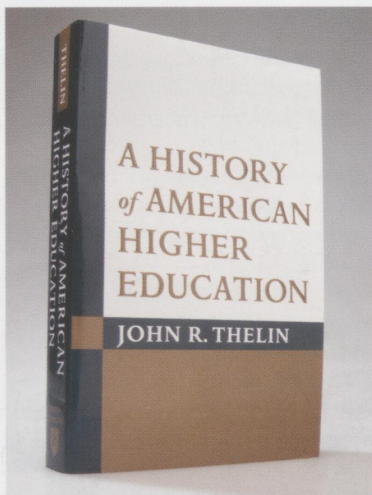


Jennifer
Swanberg

Book End

The Evolution of the American University

A History of American Higher Education
by John R. Thelin
John Hopkins University Press



Imagine the University of Kentucky without a basketball team.

Imagine the University of Kentucky without a library.

In writing *A History of American Higher Education*, John Thelin, a UK professor of educational policy studies, found some startling differences between universities of the 19th century and universities of today.

"One of the interesting things I found was that a lot of activities that seem totally normal today at our colleges and universities were in the past resented by college officials," says Thelin. "For example, athletics, studying modern languages, reading fiction, reading about and studying current events, even libraries. It wasn't until the turn into the 20th century that these activities were accepted."

The 19th-century college faculty and administration, he explains, usually had reservations about any student-initiated activity because it meant the faculty and administration were not in control. Inter-collegiate sports—involving travel to other institutions—were often seen as a nuisance and distraction. "Eventually, presi-

dents embraced sports because of their public-relations and fund-raising appeal," Thelin says, with a smile taking shape as he delivers the next line, "and as a sideshow to keep alumni and students happy and busy."

OK, sports. But why would university administrators resent a well-stocked library?

"Most mid-19th-century college presidents and their staff were preoccupied with order and accountability. Intellectual and literary exploration by undergraduates was distrusted and discouraged."

During his six-year-long investigation, Thelin drew on official institutional histories, biography, fiction, memoirs, legends, newspapers, government reports, and movies. And he was often surprised by what he discovered, saying that surprise is the scholar's delight.

"I discovered that larger universities in the early 20th century were architectural showpieces that attracted people for hundreds of miles around. Yale University, for example, attracted gawkers by the thousands who would marvel at the eight-story-high gymnasium, with its Gothic towers and gargoyles, which included two Olympic-sized swimming pools and even an indoor polo practice field."

Thelin dispels a number of myths that have been fueled by previous histories of higher education. For instance, there's the "historical fact" that several colonial colleges, including Harvard, were created to educate the clergy. Not true, says Thelin. "No, these colleges didn't, in fact, offer divinity degrees, nor did they ordain ministers."

And here's another myth: The Civil War was responsible for curtailing the development of colleges and universities, especially in the South. Not true, says Thelin. "Actually, the war provided the opportunity for Congress to pass the 1862 Morrill Land Grant Act, and this led to the creation of even bigger public universities."

Thelin took on this project as a continuation, of sorts, of Frederick Rudolph's *The American College and University: A History*, published in 1962. This has been the book on this topic for 40 years. "But its limitation became more and more obvious as the years rolled by. Obviously, a lot has happened in higher education since 1962," Thelin says, adding that he deliberately started from scratch in writing his book.

Thelin says that while he is happy to have finished this book, he doesn't believe it's the final word on the subject. "Notice that I titled it *A History of American Education*, not *the history*," he says. "I welcome disagreements because I think on a lot of these issues there is no single answer. I hope this book triggers more and better discussions about the development of higher education in his country."

The Johns Hopkins University Press has nominated Thelin's book for three national awards: The Ellis Hawley Award from the Organization of American Historians, the Merle Curti Award from the Organization of American Historians, and the Outstanding Book of the Year, awarded by the History of Education Society.

Parting Shots

"America believes in education: the average professor earns more money in a year than a professional athlete earns in a whole week."

—EVAN ESAR

"Education's purpose is to replace an empty mind with an open one."

—MALCOLM FORBES

"Human history becomes more and more a race between education and catastrophe."

—H. G. WELLS

"Education is not the filling of a pail, but the lighting of a fire."

—W. B. YEATS

"Education is a progressive discovery of our own ignorance."

—WILL DURANT

"I have never let my schooling interfere with my education."

—MARK TWAIN

"I was thrown out of college for cheating on the metaphysics exam; I looked into the soul of the boy sitting next to me."

—WOODY ALLEN

"Americans are the only people in the world known to me whose status anxiety prompts them to advertise their college and university affiliations in the rear window of their automobiles."

—PAUL FUSSELL

"The highest result of education is tolerance."

—HELEN KELLER

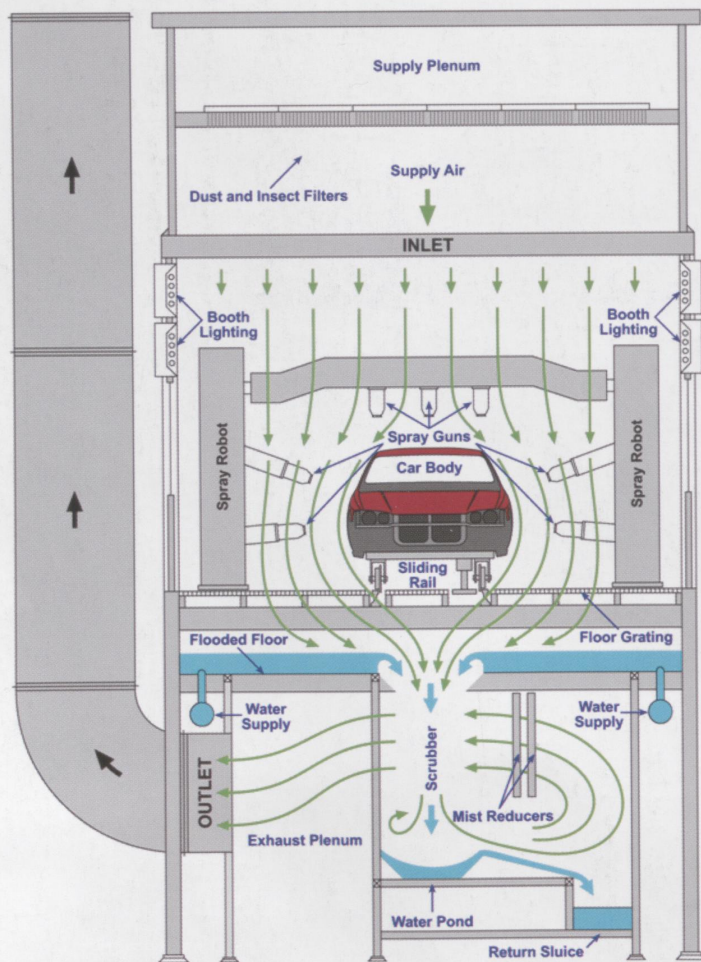
"To repeat what others have said requires education; to challenge it requires brains."

—MARY PETTIBONE POOLE

Odyssey

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