Spring 2004

Spring 2004

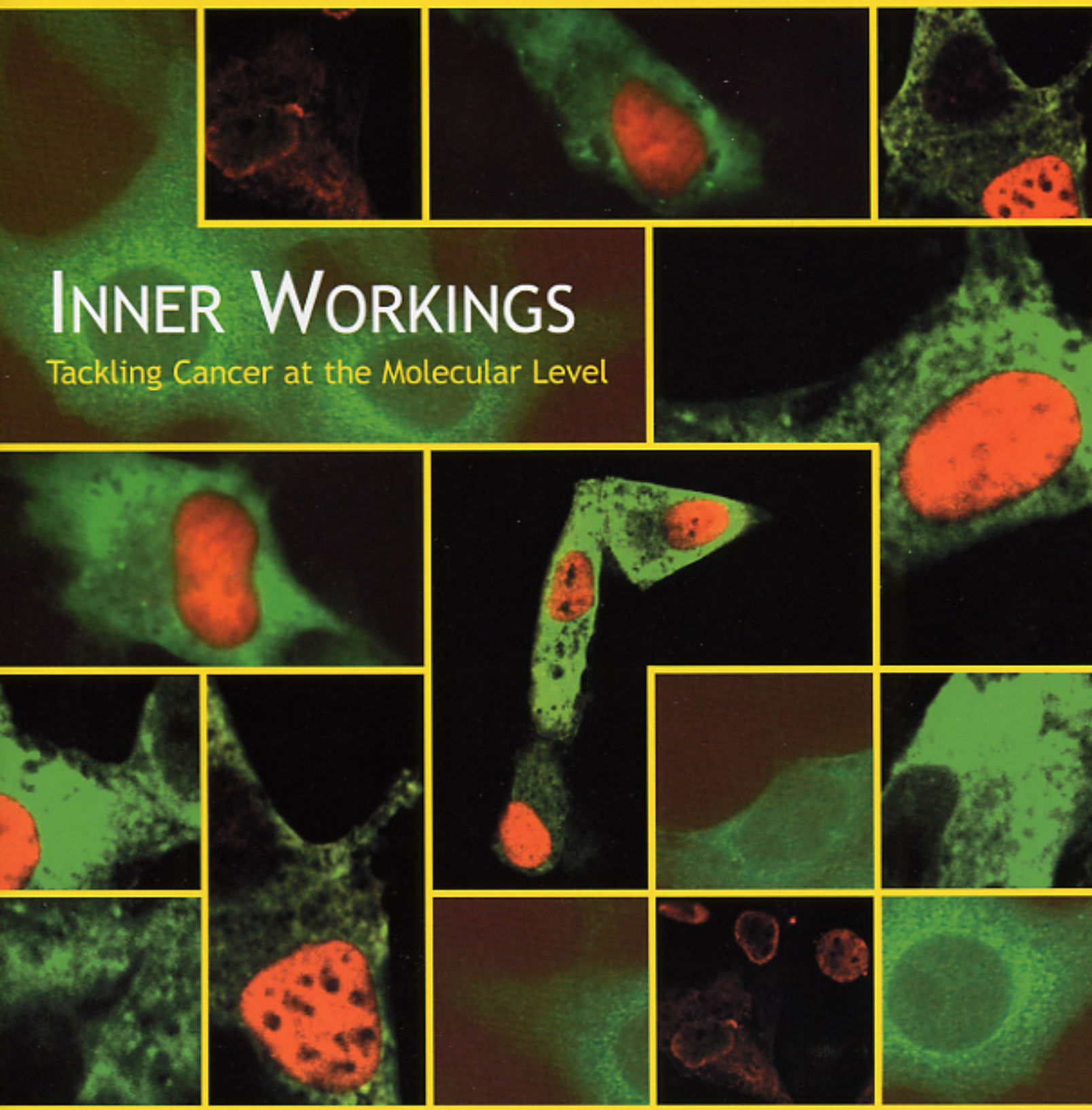
Features work by Hilla Medalia, Jodi Huggenvik, Michael Collard, Blaine Bartholomew, Lori Vermeulen, Doug Fix, Cal Meyers, Todd Winters, William Banz, Nancy Henry, Laura Murphy, Charles Fanning, and other researchers; special cover story on cancer-related research.

PERSPECTIVES

SPRING 2004

RESEARCH AND CREATIVE ACTIVITIES

SOUTHERN ILLINOIS UNIVERSITY CARBONDALE



INNER WORKINGS

Tackling Cancer at the Molecular Level

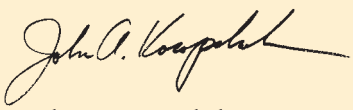
OutLook

Cancer touches all of our lives: we donate our money to help fight it; we care for our friends and family members who have been afflicted by it; we may ourselves be threatened by it. Thirty-three years after Richard Nixon launched the war on cancer, this disorder, in all its multitudinous forms, still accounts for more deaths each year in the United States than any cause except heart disease. It is a diagnosis that inevitably strikes fear.

Yet these are hopeful times for cancer research. Scientists once had only a rudimentary understanding of the genetic and cellular mechanisms that allow cancer to gain a foothold. The revolution in molecular biology has changed that. Today, researchers doing basic science—exploring the inner workings of our cells and our DNA—are finally uncovering the complexities of cancer. This new, detailed understanding is giving rise to new, improved strategies for prevention, diagnosis, and treatment.

At Southern Illinois University's Carbondale campus, we do not treat cancer patients. The clinical departments of our School of Medicine are located at the Springfield campus, which is building a new Cancer Institute for patient treatment and research. But a number of cancer-related basic science projects at Carbondale promise advances from designer drug therapy and delivery to improved diagnostic tests. This issue's special cover story describes a sampling of this research.

Bringing those applications to fruition will eventually require collaboration with clinical medicine researchers. The projects highlighted in these pages will leave another legacy, though: what they uncover about normal and abnormal cellular processes will aid the work of cancer scientists elsewhere. We are proud of our researchers' contribution and commitment to basic science that holds promise to provide new tools in the fight against this dreaded disease.



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For information about the research program at SIUC, visit www.siu.edu/~ovcr, or contact John A. Koropchak, Vice Chancellor for Research and Graduate Dean, (618) 453-4551, koropcha@siu.edu, or Prudence M. Rice, Director, Office of Research Development and Administration (ORDA), (618) 453-4531, pmrice@siu.edu.

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Photo illustration p. 7 by Esteban del Valle.

Cover: A mutant version of a protein called DEAF-1, which probably acts as a tumor suppressor in its normal form, lights up green in these fluorescent cell images. An SIUC research team is investigating DEAF-1's role in cancer. *Photographs by Philip Jensik.*

PERSPECTIVES

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The poster for Hilla Medalia's documentary shows Ayat al-Akhras at left and Rachel Levy at right.

TWO LIVES

As a home video, it's shocking. A Palestinian teenager faces the camera, a suicide note in her hand. She reads it rapidly, stridently, emphatically. One senses an undercurrent of nervousness. Her statement is short: in less than two minutes, the clip is over.

On the same day she made this video—March 29, 2002—Ayat al-Akhras left her family's home in the Dheisheh refugee camp, near Bethlehem in the occupied West Bank, and traveled the short distance to Jerusalem. There, at the entrance to a grocery store, she detonated the explosives belt she was wearing, killing herself and two Israelis. Media coverage later attributed her act to her outrage over seeing a neighbor shot to death by Israeli troops.

One of the Israeli victims that day was a girl who looked almost like her twin. Rachel Levy, who was shopping for her family's Sabbath meal, was 17. Ayat was just 18.

The news made the cover of *Newsweek*. It also preoccupied many Israeli and Palestinian youngsters, the media reported. These two girls, so similar in many ways but divided by conflict, seemed to many people to symbolize the tragedy of Israeli-Palestinian relations.

Hilla Medalia, an Israeli citizen working on a master's degree in mass communication at SIUC, was deeply affected by the news. She had already intended to do her thesis film on some angle of the Israeli-Palestinian conflict.

Medalia says she had been looking for "a story of hope, something that would break misconceptions" and hold out the hope of Israeli-Palestinian co-existence. In media interviews, she listened carefully to what the parents of Ayat and Rachel had to say. Some of their comments, she thought, undercut the stereotype of hatred that so many people have of Israelis and Palestinians.

Medalia knew that she wanted her thesis project to give voice to the feelings on both sides of the conflict. She wanted to focus on individual experiences rather than politics, and she thought that viewers would be able to relate to these two young women and their families. Through their story, she says, she hoped to give U.S. audiences "a feel of what life is like in the Middle East: one side lives under a humiliating military occupation, while the other lives under the daily threat of terrorism."

In fall 2002, Medalia persuaded both sets of parents to grant her interviews. She obtained press credentials from the Israeli government for herself and two fellow students in the College of Mass Communication and Media Arts: master's student James Saldana and undergraduate Chrissy Mazzone. They traveled with her to Israel to shoot footage over the semester break.

The result is "Daughters of Abraham." The title refers to the fact that Abraham is the founding patriarch of both Judaism and Islam.

Although the film includes some historical background, it gives the conflict a human face by concentrating on the personal lives of the girls and on their parents' reactions to the bombing. Medalia directed, produced, and edited the 45-minute documentary.

Political realities intruded on the filming. Medalia had hoped to bring the two sets of parents together, but the Israeli government would not allow Ayat's parents to travel to Jerusalem, and Rachel's parents would not enter the refugee camp. Medalia knew it would not be safe for her, either, in the camp.

So Saldana and Mazzone shot the footage there, and a Palestinian friend, Adnan Tahah, conducted the interview with the Palestinian parents for her.

The interview with Rachel's parents was in English. But back home, Medalia was faced with the thorny problem of translating the lengthy interview with Ayat's parents before she could edit that footage. "I can understand a little Arabic, but that's about it," she says.

Fortunately, around this time she met Imad Samarah, a Palestinian doctoral student in management information systems. He agreed to

do the translations—quite a time-intensive commitment.

"It took us over 50 hours," says Medalia. "Translating Ayat's video was even more difficult because she was quoting from the Koran, and Koranic Arabic is very different from contemporary spoken Arabic."

Both interviews reveal a gamut of emotions, from hatred to empathy. Both clearly express bitterness about the years of bloodshed, not just about this particular tragedy, but both also communicate a desire for peace. They hint at a hope for understanding and co-existence.

That certainly is Medalia's hope. It is one reason she chose music by Sheva—a band made up of Muslim, Jewish, and Christian Israelis and Palestinians—to score the documentary.

The filmmaking process, she says, "was very hard. Not just because of all the hours in the editing room [agonizing over what to cut]. The conflict is something I live every day. Making the film gave me a much deeper understanding of it."

An early, 10-minute cut of the documentary won Medalia a Carole Fielding Student Grant, a national award from the University Film and Video Association. (She is the first SIUC student so honored.) This $2,000 grant helped fund the work in progress.

Medalia had some additional financial support from Carbondale's Jewish community. Beyond that, she spent several thousand dollars from her own pocket—charging expenses and getting grocery money from her parents so she could put much of her graduate assistantship stipend toward the film. Her parents also helped out during filming, allowing the crew to stay at their house and providing transportation.

Radio-television professor Jan Thompson was "the force behind everything," Medalia says. "When we went to Israel to shoot, we had legal issues, because Chrissy was only 19. Jan took care of getting the permissions we needed.

"She pushed me—gave me deadlines that I thought were impossible. So I'd go off and just work [and get it done]. Some days I wanted to give up—I was sick of sitting in the editing room. But she was very supportive."

"Daughters of Abraham," which Medalia completed in September 2003, has been screened at SIUC and several other universities.

Medalia graduates this spring with her M.A. in professional media practice. She plans to return to Israel after gaining some job experience in film or television.

For more information: Hilla Medalia, hillam15@siu.edu, or c/o Jan Thompson, Dept. of Radio-Television, (618) 536-7555, janione@siu.edu.

—Marilyn Davis

▲ Top: Chrissy Mazzone, a senior in radio-television, films on location in the Dheisheh refugee camp in the occupied West Bank.
▶ Right: Hilla Medalia shoots footage near Tel Aviv.

SHUTTLE DIAGNOSTICS

America's space program is benefiting from the expertise of an SIUC faculty member.

Tsuchin Philip Chu, an associate professor of mechanical engineering and energy processes, regularly works with NASA scientists and engineers to help solve complex problems. His current project, funded through a $30,000 collaborative grant, involves developing a software system for more precise detection of hydrogen leaks in the nozzle of the space shuttle main engine.

The engine nozzle contains more than 1,000 metal alloy tubes, each about the diameter of a straw, which run through its length. They are attached to a stainless steel jacket lining the inner wall of the nozzle.

Liquid hydrogen is pumped through the tubes to cool the nozzle while it is firing. The hydrogen eventually flows into the main combustion chamber, where it is used as fuel.

During flight, cracks or tiny holes can develop in the tubes from stress, temperature changes, or corrosion, Chu explains. Those defects allow hydrogen to leak into the spaces between the tubes and the jacket.

Although no space shuttle accidents have resulted from such leakage, NASA knows that it occurs. Inspection teams routinely detect leaks after a shuttle flight. The situation poses a real danger: if cooling efficiency were reduced too much during flight, serious engine problems could result—not to mention the fact that leaked hydrogen could explode.

NASA inspects and tests the main engine nozzles after each flight before they are sent to Florida for installation on another shuttle. Newly manufactured nozzles are checked extensively as well. Chu's software will aid this inspection process by enabling engineers to zero in on leaks and repair defective tubes.

The current procedure for detecting the location of leaks is inexact and "very tedious," Chu says. "They may have to open up 20 or 30 tubes to insert a [detection] scope, and they still may not find the leak."

Chu is part of NASA's "nondestructive evaluation" (NDE) team, which develops better, faster, noninvasive ways to inspect shuttle parts. In this case, leaks in the coolant tubes can be pinpointed with thermography—detecting and analyzing slight temperature changes using an infrared camera system and image analysis software. Chu is developing the software for a new camera system that NASA is implementing.

"We can detect the exact location of the leak and can do it faster and without cutting tubes," he says. "Once the detection system is in place, you can save a lot of money, because you can inspect a large area at one time."

"Right now [our] evaluation techniques give us a general area," says NASA spokeswoman June Malone. "Dr. Chu's software is going to give us more accuracy. That will save a lot of time if you can pinpoint exactly where a leak is coming from."

Chu has been traveling back and forth to the Marshall Space Flight Center in Huntsville, Ala., to work on the new system. The project will last through October 2004.

Chu's collaboration with NASA engineers dates to 1994, when he participated in the NASA Faculty Fellowship Program, a 10-week summer research residency. An expert on composite materials and image analysis, Chu has held a number of other NASA grants and has worked at the Marshall Space Flight Center almost every summer since 1997 on thermographic inspection modeling and other projects.

For more information: Dr. Tsuchin Chu, Dept. of Mechanical Engineering and Energy Processes, (618) 453-7003, tchu@siu.edu.

—Pete Rosenbery

▲ This launch photograph gives a good view of the nozzles of the space shuttle's three main engines. Tsuchin Chu's new software will better enable NASA engineers to pinpoint hydrogen leaks in the nozzles. *Photo by NASA.*

GREENER ALTERNATIVE?

Given today's environmental and economic realities, SIUC researchers think it's time to take a fresh look at propane for use down on the farm.

"It's readily available, the infrastructure is already here, it burns cleanly, and it's an alternative fuel source—it reduces our dependence on oil from the Middle East," says Tony Harrison, an agricultural systems expert in SIUC's College of Agricultural Sciences.

"Is it better than the old reliable—diesel—that's been around for decades? Our job is to take it out in the field and see.

"We're going to collect data in our engine lab, then put it out there and look at how it performs under farm conditions so that we can say if it's all it's made out to be—and have the data to support what we say."

Harrison and his colleagues Dennis Watson and Richard Steffen will test the relative benefits of propane and diesel fuel in a study involving an irrigation system. A $487,000 grant from both the state and national propane councils is underwriting the two-year project.

"The small engine industry is eagerly awaiting the results," says Bernard Sieracki, who serves on the national council's agriculture advisory committee. "Nothing like this kind of direct comparison has ever been done before."

The three researchers are setting up a center-pivot irrigation rig—one of those elevated, rolling watering lines that circles around a fixed point—on a 40-acre field southwest of campus.

In running the system's pump and pivot, automated equipment will switch between propane and diesel engines during each watering period, using an innovative hydraulic system to allow each to operate at peak efficiency.

"This lets us compare apples to apples," Harrison says. "If we test diesel one day and propane the next, we're not running under the same temperature and relative humidity—and those affect what the engine is doing."

Electronic monitors will keep track of emissions, fuel flow, efficiency, and other data. In the project's final phase, the researchers will set up wireless transfer of information back to campus so they can upload the data on the project's Web site.

Site visitors will be able to look at results from just one of the power sources or compare the two—on a particular day, week, month, year, or over the life of the entire project.

The project's near-real-time feature and its automated control and monitoring systems should make it a desirable test site for other kinds of power sources, Harrison says. According to Sieracki, it is the only test bed of its kind in the United States.

For more information: Dr. Tony Harrison, Dept. of Plant, Soil, and Agricultural Systems, (618) 453-6985, tonyh@siu.edu.

—K. C. Jaehnig

Canola could make a comeback in the heartland's fields.

"The biggest problem has been to identify winter-hardy varieties that would stand up consistently to Midwestern conditions," says Anthony Young, professor emeritus in the College of Agricultural Sciences.

"We have just now gotten to the point where we are consistently getting good survival rates for 10 or 12 varieties. Our mission over the next few years is to increase the acreage grown."

Young heads the Midwest Regional Canola Research Program, one of six such programs set up a decade ago by the U.S. Canola Association to solve regional production problems. His region consists of 19 states, with scientists from SIUC and four other universities conducting the research.

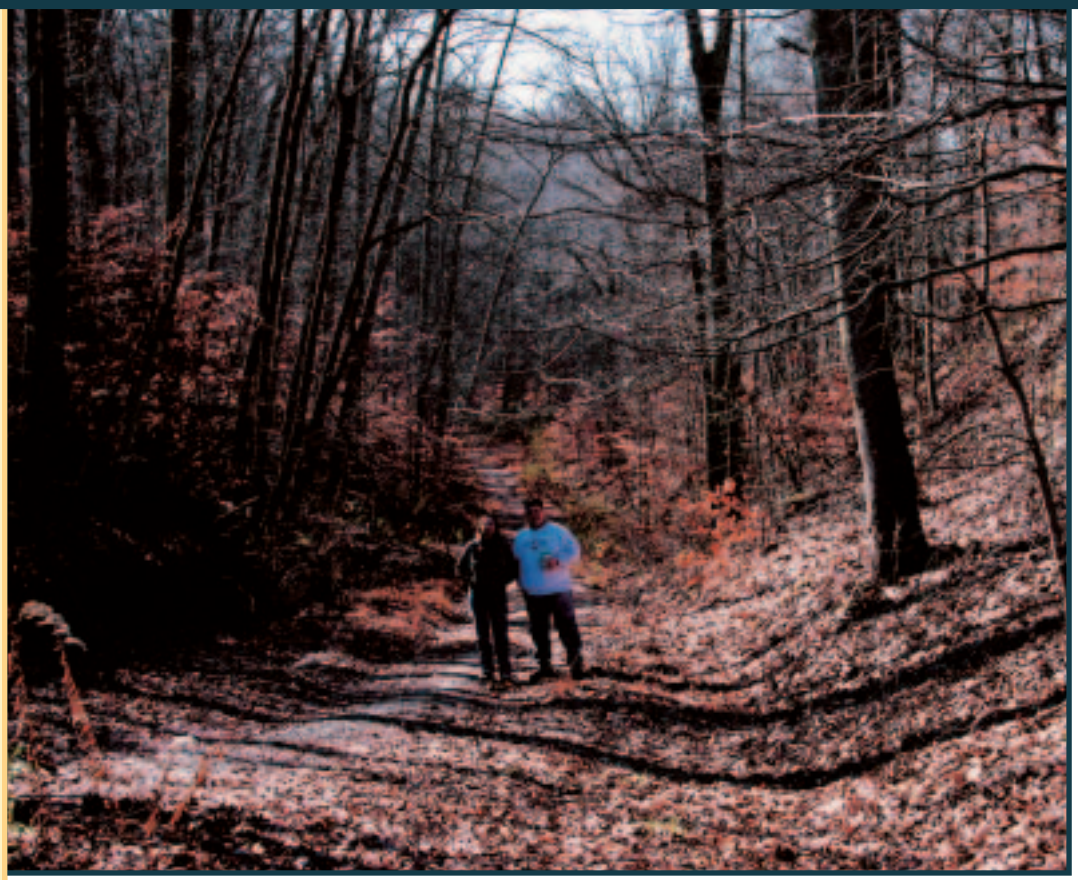
Demand is high for canola, whose oil is rich in heart-healthy omega-3 fatty acids, but growers in this country can't begin to meet the need. The United States imports nearly all of the canola it uses.

Canola got a bad reputation in southern Illinois during the late '80s and early '90s, when farmers lost virtually their entire crop several years running. That won't happen again, Young believes.

"We have taken about 400 lines developed out of the Kansas State University breeding program and tested them under local conditions," he says. "We are also taking the best of these and making crosses with some of our local varieties." One of those crosses will soon be released into national variety evaluation trials.

"With all that effort and the success we've had, we are now ready to go back to the producers and say, 'We will work with you to get the right varieties for your situation.'"

—K. C. Jaehnig



Trail spotters: Karen Frailey, a graduate student in forestry, and Steven Fadden, former site superintendent of Union County Refuge, take a short break from hiking the Trail of Tears near Atwood Tower in the Shawnee National Forest.

TRAIL OF TEARS

They called it the Trail of Tears because of the losses suffered by the exiles whose weary feet created it.

Then it, too, was lost.

"If you know what you're looking for, you can see it—it's just so obvious—but unfortunately, most people don't know what it is," says John Burde, an SIUC forestry professor.

Burde and graduate students Karen Frailey and Kevin Schraer have spent the last few months tracking down the Illinois leg of the trail at the behest of the National Park Service, which is working to preserve and develop the paths that 19th-century soldiers once used to drive Cherokee Indians off their land.

The Trail of Tears—actually three overland routes and a waterway—begins near Chattanooga, Tenn., and ends in Oklahoma. Rounded up like cattle and stripped of their property under the federal Indian Removal Act of 1830, thousands of Native Americans were forced to march west on the trail through winter storms. Many died. Congress made the trail a national historic area in 1987 to honor them.

Only a small piece of the trail's northern route runs through Illinois, from Golconda to a point just north of Cape Girardeau.

"Unfortunately, a lot of it is right under the existing highway—those parts are gone," Burde says, referring to Illinois Highway 146. "A lot of it has been plowed under for agriculture, too.

"But there are numerous places not far from 146 where the original road is quite obvious. We've pretty much identified the trail except for a piece west of Jonesboro."

After reviewing aerial photographs in fall 2003 to identify segments of the trail, Burde and Schraer began mapping it on foot, using hand-held global positioning system (GPS) equipment that takes measurements every five seconds. The equipment translates radio signals from satellites into geographic information. The mapping had to be done in the wintertime because thick foliage can interfere with the signals.

Fellow faculty member Andrew Carver and his students in the Forestry Department's Geographic Information System laboratory will use the data to create detailed maps showing trail segments, topographic information, land use patterns, and political boundaries.

Burde's team also is digging through archives and libraries, hoping to root out old maps, newspaper articles, letters, diary references, and other materials about the trail in southern Illinois. Whatever they find will go into an annotated bibliography, something that could be used not just by researchers but by regular folks who want to learn more about the trail.

"There's a lot of interest down here, a lot of community lore, and a lot of people claim kinship to the Cherokees because they stayed some time in certain areas—they didn't just pass through," Burde says.

"We've already found some articles from the '20s and '30s. For someone interested in looking deeper, this would be a good point to start."

The research also could help regional tourism development efforts. For example, the Park Service could use the material as the foundation to build what

Burde calls a tourist "interpretive route"—a means for following the trail and understanding what happened there.

As part of their report to the Park Service, the team will identify potential interpretive/educational sites, recreational opportunities along the trail, and ways to preserve and develop existing segments in partnership with landowners. (For her master's thesis research, Frailey will identify and interview landowners to see who might be willing to allow hikers or interpretive signs on the portions of the trail that cross their land.)

"We're behind other states in this, probably because we have the shortest number of miles—of all the states that the trail goes through, Illinois is the only one without a museum or a cooperating visitors' center where people could go to find out about it," Burde says.

"But that doesn't make Illinois less important. Serious winter events occurred here. When the Cherokee got over toward the river—in November or December—the Mississippi was iced over and they couldn't get across, so they had to set up camps. A lot of people died.

"There's a fairly large church cemetery east of Anna that has no headstones. The common lore is that those are Cherokee graves, but nobody knows.

"Even with history, some things get lost. That's why the Park Service has started this project."

For more information: Dr. John Burde, Dept. of Forestry, (618) 453-7463, jburde@siu.edu.

—K. C. Jaehnig

WEIGHT ON THEIR MINDS

Kids across America are stressing out about how much they weigh, worried they'll become super-sized like many of the adults they see, according to a new national survey of 9- to 13-year-olds conducted by health education experts at SIUC.

Results show that 59 percent of the more than 1,100 youngsters surveyed have already tried to lose weight; 54 percent worry about their weight; and 52 percent agree there's a problem with kids being overweight today.

Health education professors Stephen Brown and David Birch conducted the survey on behalf of KidsHealth - KidsPolls, a consortium that gives children a national platform to share their views on health-related issues that affect them.

On the upside, says Birch, "children seem to be hearing the many messages and warnings being issued about obesity and all the attendant problems it can cause."

Brown says that this heightened awareness couldn't come at a better time. About a third of all American kids are either overweight or at risk of becoming so—three times the percentage that were 20 years ago, according to statistics gathered by the Centers for Disease Control and Prevention.

On the downside, however, the survey uncovered some excessive concern about body image and achieving thinness.

Among other findings:

- Of the youngsters surveyed, approximately 22 percent reported being slightly or very overweight, and 23 percent said they weigh less than they should.
- Fifty-six percent said someone has spoken to them individually about their weight.
- While 55 percent of youngsters said they are at about the right weight, more than half of that group—57 percent—admitted they've tried to shed a few pounds.
- A surprising 43 percent of the kids who said they are "slightly or very underweight" also have tried to lose weight.
- Sixty-seven percent of girls said they worry about their weight, compared to 41 percent of boys.
- Sixty percent reported that it's harder for overweight kids to make friends.
- Sixty-nine percent believed that healthy eating and exercise are the best ways to control weight; only 17 percent thought dieting is more effective.

Responses to the survey were gathered in November 2003 from children visiting nine different health education centers around the country. The youngsters live in large and mid-size cities, suburbs, and rural areas, and their ethnicities mirror U.S. averages.

KidsPolls are a cooperative project of the National Association of Health Education Centers, the Nemours Center for Children's Health Media (the creators of KidsHealth.org), and SIUC's Department of Health Education and Recreation.

For complete survey findings and methodology, visit http://nahec.org/KidsPoll/.

—Paula Davenport

KUDOS

▲ John Y. Simon

▲ Yong Gao

▲ Boyd Goodson

• History professor John Y. Simon, executive director of the Ulysses S. Grant Association, received a 2004 Lincoln Prize for outstanding achievement for the landmark *The Papers of Ulysses S. Grant.* This scholarly edition of Grant's correspondence and other writings currently stands at 26 volumes.

Simon has worked on the project since its inception in 1962. "It has been an opportunity for me to spend time with a spectacular figure in American history," he says. "Grant was a complex character—an unmilitary soldier, an unpolitical president and an unliterary author."

The Lincoln and Soldiers Institute at Gettysburg College administers the Lincoln Prizes.

• The National Science Foundation's prestigious Faculty Early Career Development Award has gone to two more assistant professors in SIUC's Department of Chemistry and Biochemistry, bringing its number of CAREER Award holders to four. Yong Gao won $465,000 for research on using magnetic nanoparticles to recycle reagents, catalysts, and other chemical compounds by extracting impurities. Boyd Goodson won $550,000 for research on using lasers and liquid crystal solutions to enhance nuclear magnetic resonance (NMR) studies of molecular structure and dynamics.

• A highly competitive $30,000 media grant from the National Endowment for the Humanities will enable Tom Godell, associate director of SIUC's Broadcasting Service, and Jan Thompson, assistant professor of radio-television, to research and write a treatment for a two-hour documentary about influential 20th-century conductor Serge Koussevitzky.

• SIUC's 2003 Outstanding Dissertation award went to Saikat Talapatra, who earned his Ph.D. in engineering science. Working in the lab of physics professor Aldo Migone, Talapatra did groundbreaking research on the mechanisms by which gas atoms adsorb (bind) to bundles of carbon nanotubes. These tiny tubes, whose walls are only one atom thick, may someday be used in energy systems to store hydrogen.

Among other things, Talapatra determined the location of adsorption sites, the surface area available for adsorption, and the binding energy of various gases. His lab experiments also showed that gas atoms adsorbed to nanotubes behave like one-dimensional matter. Milton Cole, a theoretical physicist at Pennsylvania State University, has called the discovery "a landmark contribution to science."

• Anthropology master's student Haagen Klaus won the SIU Alumni Association's 2003 Outstanding Thesis award for his excavation and analysis of a pre-Incan metal and ceramic workshop and associated cemetery on the north coast of Peru. By studying the type, quality, and placement of grave goods at the 1,000-year-old site, as well as analyzing the human remains for indicators of health and diet, Klaus made the case that burial practices varied with the ethnicity and status of the deceased. Izumi Shimada, the anthropology professor with whom he worked, says that Klaus's work "constitutes an important contribution to the rapidly expanding field of bioarchaeology."

▲ Haagen Klaus (at right) and a Peruvian crew member excavate a pre-Incan grave. *Photo by Izumi Shimada.*

EXECUTIVE BEHAVIOR

▲ **Asked by neuropsychologist Kimberly Espy to identify a shape by its color only if it's not wearing a hat—and to ignore all shapes that have frowny faces—four-year-old Mitchell Kaufmann has to stop and think.**

How preschoolers develop self-control is the focus of a new five-year, $1.65 million study at SIUC.

"There are a number of disorders [relating to self-control] that emerge in the preschool period, attention deficit disorder and autism being two of the best known," says Kimberly Andrews Espy, associate professor of family and community medicine in the School of Medicine and head of the research team conducting the study.

"Part of the reason the National Institute of Mental Health funded this project is that we know so little about how [self-control] develops. If we can understand it in garden-variety children, it will help us understand how these other children get off the path."

Earlier work in Arizona with toddlers exposed prenatally to cocaine sparked Espy's interest in how children in general develop self-control. The development that takes place in children between the ages of 3 and 6 is "dramatic," she notes.

"They move from being impulsive, in-the-moment kids who can't wait for anything to children who can sit in a classroom, who can get their needs met through speaking, who can follow complex directions. The scientific label for this is 'executive control,' because they, like executives, can manage or guide their behavior purposefully to achieve a goal."

Espy's project ultimately will involve some 400 youngsters from all over southern Illinois. Half of them will undergo monitoring at nine-month intervals from their third birthdays until their sixth. A smaller group of 40 to 50 children will be added at each nine-month interval, with regular observation periods continuing until their sixth birthdays.

"We wanted to have groups coming in at staggered periods in order to separate how much of the result is due to development and how much is due to [their] having done the tasks over and over again," Espy explains.

Researchers will watch the children perform three sets of three tasks, each aimed at measuring such functions as memory and inhibition. In one such task, for example, children have nine chances to search for treats hidden under cups; the better they remember where they searched previously, the more treats they can find—and eat.

Sessions will be videotaped so that the researchers can later record how many times the children got out of their seats, didn't pay attention to the task at hand, and so forth.

While children are taking the hour-long battery in Espy's lab, their parents will meet with members of Espy's research team, answering questions about the kids' actions and behavior at home and at school. That will give the team a fuller picture of each child's development.

Neuropsychologist Paul Kaufmann, currently working on a law degree at SIUC, helped develop some of the task sets, a host of research assistants are conducting the sessions, and University of Houston psychologist David Francis will assist with data analysis at the end of the three-year testing period.

"Preschoolers are fun to work with," says Espy, who also heads a five-year federal study on the effects of prenatal nicotine exposure on child development.

"They're spontaneous, they try their best, and they say funny things. It's my favorite age."

For more information: Dr. Kimberly Andrews Espy, (618) 453-1855, kespy@siumed.edu.

—K. C. Jaehnig

Inner Workings

Researchers at SIUC are tackling cancer at the molecular level. Some of their work promises potential applications for diagnosis and treatment; all of it adds to the pool of knowledge that scientists worldwide tap for insights and answers. Wade on in as we tour cancer-related projects on SIU's Carbondale campus.

Story by Marilyn Davis
Photographs by Jeff Garner,
Russell Bailey, and Steve Buhman

Cancer is a disorderly affair in which cells go out of control—proliferating rapidly, refusing to die, overwhelming the body's defenses, and eventually growing into tumors.

To fight the scourge of cancer, SIUC researchers in science, medicine, and agriculture are working at the molecular level. Their research explores fundamental biological processes; it goes by the heading of basic science. But some of these projects are leading to possible applications—holding out the hope of improved diagnostic tests, new cancer therapies, and custom-designed materials for drug-delivery systems.

Understanding each complex piece of the cancer puzzle takes years. Sometimes leads that seem promising fizzle out. But negative results can be as important as positive ones, because they help scientists refine their efforts. One way or another, by indirect and sometimes surprising means, molecular-scale explorations in the lab eventually pay off in the doctor's clinic. The key to the war on cancer is understanding what can go wrong with the intricate dance genes and proteins do, every day, to keep us alive—and how to counter what goes wrong.

The right stuff

To do their job, genes must be *expressed:* translated into proteins. In a process called transcription, the DNA in our genes acts as a template for the assembly of RNA molecules. These RNA molecules shuttle off to special areas of the cell, where they in turn serve as templates for the assembly of proteins from amino acids. Proteins drive the business of the cell—and thus the business of life and death.

Genes must be expressed at the right times and to the right degree. If the wrong proteins are being made at the wrong times, or in the wrong amounts, it opens the door for all kinds of trouble, including cancer. Special proteins called transcription factors govern gene activity, latching on to genes and controlling their expression. These factors regulate protein levels in the cell by boosting, decreasing, or shutting off RNA transcription.

SIUC physiology professors Jodi Huggenvik and Michael Collard, who study biological processes at the molecular level, have been teasing out the function of a transcription factor called DEAF-1, which plays a crucial role in embryo development and neuron functioning. Their research strongly suggests that it also is connected with cancer.

"Genes involved in embryonic development need to be on during a very specific time and then usually need to be shut off—you don't need them as an adult," Collard says. "DEAF-1 may function in shutting off these very powerful genes that drive development. That can relate to cancer: if you have mutations in DEAF-1, then genes that should be suppressed may get activated."

DEAF-1 was first identified in 1996, in fruit flies. In 1998, Rhett Michelson, one of Huggenvik's doctoral students, stumbled across a similar transcription factor in monkey cells. The SIUC research team soon identified the same factor in human and rat cells and eventually determined that it was the mammalian version of DEAF-1. (Researchers have since identified DEAF-1 in other species as well; it probably occurs in all animals.)

"We got very excited about this transcription factor," Collard says, "because when we

In these fluorescent cell images, a protein called DEAF-1 lights up red. DEAF-1, which helps regulate DNA transcription, may function to suppress the development of cancer. ***Photo by Philip Jensik, courtesy Michael Collard.***

Jodi Huggenvik and Michael Collard are investigating whether a gene called DEAF-1 normally acts to suppress tumor formation and what may happen to "switch off" that gene in certain cancers.

Doctors might be able to use DEAF-1 levels to more accurately diagnose prostate cancer and gauge a patient's prognosis.

looked at its amino-acid structure, we saw similarities with a number of other transcription factors that are involved in cancer." When the researchers studied the chemical sequence of the DNA that codes for the DEAF-1 protein, their suspicions were reinforced.

They also found evidence of a cancer connection in GenBank, a worldwide database that archives DNA sequences from around the world. "People have submitted DNA sequences from cancer patients that correspond to DEAF-1, but we find that these sequences are often mutated," Huggenvik says.

Putting the brakes on cancer

DEAF-1 may be a tumor suppressor—a gene that puts the brakes on cancer. In cell experiments, Huggenvik and Collard have found that the DEAF-1 protein normally suppresses a particular gene which is overexpressed in lung cancer. The research team now is deleting the DEAF-1 gene from specific tissues in mice to see if cancer results.

If DEAF-1 is indeed a tumor suppressor, mutations may destroy its anticancer power. In fact, says Collard, "If we mutate DEAF-1 [in test-tube experiments], it seems to act like an oncogene—a gene that drives cancer."

Huggenvik and Collard's early research on DEAF-1 was funded by the American Cancer Society and by internal SIUC grants. In 2001 the National Cancer Institute awarded the two scientists a five-year, $1.17 million grant to investigate whether DEAF-1 is a tumor suppressor for Wilms' tumors, a type of kidney cancer in children.

One clue in that regard relates to gene inheritance and expression. We inherit two copies of each chromosome and hence two copies of each gene—one from our mother and one from our father. Usually both copies of a gene are expressed in the cell. Having this diversity is like having an insurance policy: if one copy of the gene becomes damaged, the cell has a backup.

In the case of a few genes, however, only the maternal or only the paternal copy is expressed. In gene-speak, the other copy is "silenced." These are called imprinted genes.

Imprinting must serve some important physiological purpose, because it comes at a high price: no backup. The silenced copy of the gene can't take over if something goes wrong. And cancer is a classic case of that.

As tumor cells divide and multiply, they often kick out "normal" copies of genes and duplicate mutated or silenced copies. It's significant, then, that cells from Wilms' tumors almost always contain two paternal copies of the chromosome region where DEAF-1 is found—and no maternal copies. This chromosome region may host an imprinted tumor suppressor gene that ends up totally silenced in Wilms' tumors because the active copy is missing.

Huggenvik and Collard think that DEAF-1 is the most likely candidate for that tumor suppressor gene. Certain complexities in the way it's transcribed suggest it is an imprinted gene, and the chromosome region where it's located—the tip of the small arm of chromosome 11—contains other imprinted genes. This region of chromosome 11 seems to be mutated or silenced in many human diseases, including ovarian, lung, colon, breast, and prostate cancer.

DEAF-1 and prostate cancer

While Huggenvik and Collard continue to test that hypothesis, a new National Cancer Institute grant is allowing them to explore DEAF-1's role in prostate cancer. Co-investigators Kounosuke Watabe and Thomas Tarter,

faculty at the SIU School of Medicine in Springfield, are establishing a tissue bank for this study and helping to analyze protein expression in cells.

In pilot work, the team found that DEAF-1 levels were low or nonexistent in half of the prostate tumor samples they analyzed. The lower the levels, the less likely the patient was to survive.

If these early findings hold up in wider-scale testing, doctors might soon be able to use DEAF-1 levels to more accurately diagnose prostate cancer and gauge a patient's prognosis—information that could influence treatment.

Huggenvik and Collard also will try to determine what causes decreased levels of the DEAF-1 protein in prostate cancer. It could be due to gene mutations. But there is another possibility that holds more promise for patients.

Genes are sometimes switched on or off when they shouldn't be because chemical units called methyl groups have bound to them. "The main way gene imprinting seems to be regulated is through DNA methylation," says Collard. In some types of cancer, in fact, it's already known that a tumor suppressor gene is being silenced because of DNA methylation.

"Right now, in clinical trials, [biomedical researchers are] trying chemicals that might interfere with methylation," Collard adds. "They're hopeful that when genes get silenced [in the disease process], they can turn them back on, and vice versa." If the DEAF-1 gene is being silenced through methylation in prostate cancer, perhaps some type of drug treatment could reverse it.

Packing and unpacking

Also working at the gene level to tackle cancer is molecular biologist Blaine Bartholomew. Although Bartholomew began his career by studying transcription factors, recently he's been zeroing in on the cellular processes that make transcription possible to begin with.

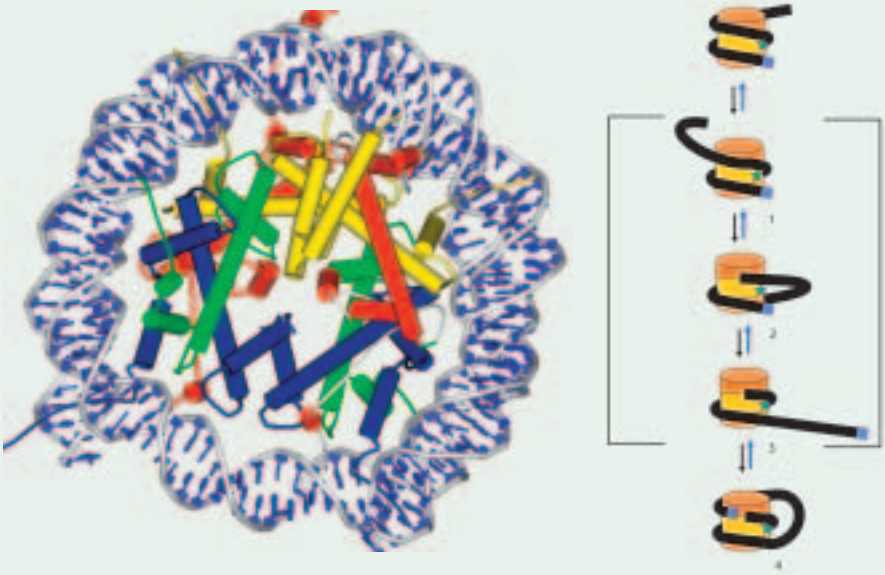
Problems there, like problems with transcription itself, can result in cancer. Bartholomew's research has been funded by the National Institutes of Health for 14 consecutive years, a remarkable record, and by the American Cancer Society.

Most of us know the familiar illustration of DNA as a long double helix trailing down the page like a ribbon. DNA is a double helix, all right, and it is an incredibly long molecule. But in real life it doesn't exist in a leisurely, relaxed state.

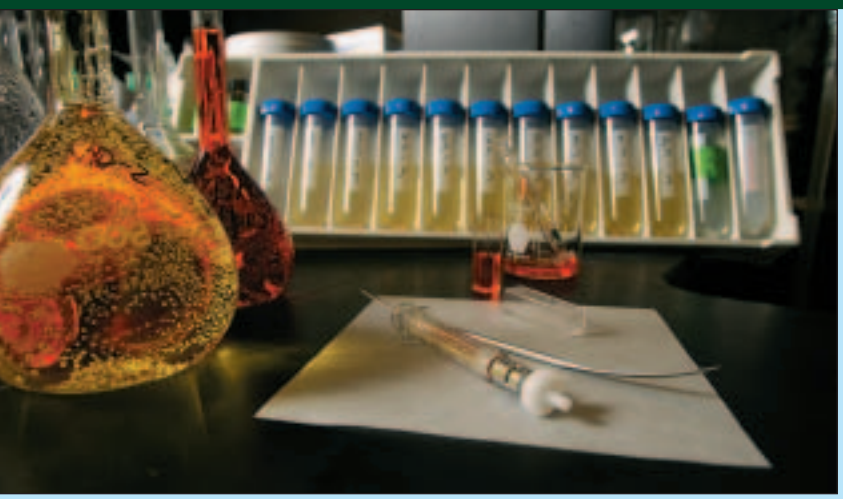
"If you lined up our DNA in one straight line, it would be about one meter long," says Bartholomew. "In order for it to fit into the nucleus of the cell, it has to be compacted several thousandfold."

Small packaging proteins called histones bind to the DNA and compact it. The long strand of DNA winds around thousands and thousands of these histones, like little spools wrapped with one long piece of thread. To condense things even more, the whole assembly of histones is twisted together tightly, resembling a beaded necklace that's been knotted up. This gnarly skein of DNA and proteins is chromatin—the stuff that makes up our chromosomes.

The cell's compacting scheme works wonderfully well, but it means that much of the DNA is tucked deep inside the chromatin package. "The problem is, the cell has to gain access to DNA at certain points in its life cycle," Bartholomew says. For genes to be expressed—transcribed into RNA molecules and then translated into proteins—the cell must somehow get at the bits of DNA it needs to transcribe.



▲ This cross-section view of chromatin (above, left) shows DNA wrapping around the outside of a histone—a protein "spool." (The blue, green, yellow, and red rods represent the four different proteins that make up the histone.) Chromatin "remodeling" allows the cell to unspool DNA from a histone, freeing up a stretch of DNA so that it can be transcribed (see sequence at right). Certain cancers are linked to problems with chromatin remodeling in cells. ***Illustrations courtesy Blaine Bartholomew.***



When clay materials infused with a chemical compound are suspended in water and subjected to ultrasound, the compound is slowly released, turning the water yellow. The longer the ultrasound exposure, the more of the chemical that is released and the darker yellow the water (see the sequence of tubes from left to right). The red liquid is the original, undiluted compound.

On Target

Because chemotherapy takes such a heavy toll on the body, scientists have been working on ways to deliver drugs directly to tumor sites, bypassing healthy organs. But they'd also like a way to control the release of drugs from delivery devices. Better dosing control could decrease the side effects of toxic drugs and make treatment more effective.

SIUC materials scientist Lori Vermeulen thinks a well-known and safe material, clay, and a well-known and safe technology, ultrasound, might be used to externally control the delivery of drugs from implants or carrier medications.

An expert on designing and synthesizing layered materials and polymers, Vermeulen was familiar with studies showing that ultrasound could activate drug release from polymer implants. To exploit ultrasound as a tool for controlling drug release, she knew scientists would need to develop a broader materials base for drug delivery. She thought that natural or synthetic clays might fit the bill.

Clays, which are layered inorganic materials, can be induced to host certain organic chemical compounds ("guests") in the tiny gaps between the layers. Ultrasound, she thought, might be used to activate and control the release of guest drug compounds from clay materials.

"Things stick to clay. The idea is to stick the drug to it and release the drug the way you want to," she explains. "From a chemist's point of view, it's easy to modify the structure of the host to suit the drug."

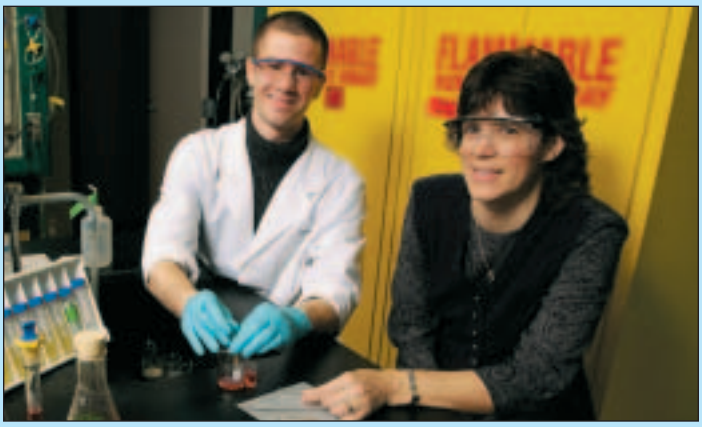
To test her hypothesis, Vermeulen's lab team introduced several different guest compounds, including two containing biologically active molecules, into samples of a clay called montmorillonite. They suspended the clay samples in water and then applied ultrasound. They found that they could affect how rapidly and completely a guest compound was released from a sample by varying the ultrasound frequency.

The team also got promising results with some synthetic clay-like materials that Vermeulen designed. These materials, called metal phosphonates, are layered like clay. But because they can be designed to carry a wider range of guest compounds, including proteins, they might prove to be a more versatile class of materials for drug delivery.

The specific chemical and physical features of each clay compound determine how these hybrid materials respond to ultrasound, Vermeulen says. For example, ultrasound breaks down the particle size of the guest compound in some of the samples, but not others. Such factors, along with environmental conditions in the body, will determine the rate and degree of drug release. But Vermeulen's research suggests that it can be regulated. And clays are biologically inert, making them a benign substance for medical use.

Vermeulen's proof-of-concept studies were funded by a grant from the American Cancer Society. Master's student Patricia Calloway, now a chemist with Eli Lilly Co., did much of the lab work and is writing her thesis on it.

Vermeulen plans to continue designing, synthesizing, and analyzing various combinations of hosts and guests and testing them with a range of ultrasound frequencies. Ben Baptist, a chemistry major, has an undergraduate assistantship to help with the research. Although their investigations are still at a very early stage, Vermeulen hopes it will be possible to design materials that can work in practice to deliver specific anticancer drugs.



Lori Vermeulen and chemistry major Ben Baptist.

Prime movers

Once again, as with transcription factors, special proteins do the job. In this case, the workhorses are so-called chromatin remodeling complexes. "These are large assemblies of proteins—protein machines, if you will—that reorganize the chromatin package so the DNA is accessible to the transcription machinery in the cell," Bartholomew says.

A remodeling complex works by glomming onto the chromatin, pushing and prodding until it uncovers the particular histone it wants. It "unpackages" a stretch of DNA by pulling it away from the histone (chromatin can expand and contract much like a telephone cord does). That allows transcription factors to get at the DNA.

Transcription takes place as chemicals in the cell bind along the stretch of DNA, self-assembling into an RNA molecule. The remodeling complex keeps "feeding out" the DNA until transcription of the needed gene is done. The completed RNA molecule then peels itself away, leaves the nucleus, and heads for the cell's protein-making factories. Mission accomplished.

"Ten years ago, it wasn't even known that these remodeling complexes existed," says Bartholomew. "Originally people thought transcription factors were all it took to control gene expression."

Now, he says, scientists know that remodeling also is critical in keeping the cell functioning smoothly. If the genes that code for chromatin remodeling complexes are mutated, developmental problems and embryo death can result. So can cancer.

"If you take the proteins that are in remodeling complexes and you mutate them in mice, you find that the mice are much more predisposed to the formation of different cancers," Bartholomew says.

"If you look at known cancers, you find that in many cases genes involved in remodeling complexes are mutated. For example, aggressive pediatric cancers are highly associated with defective chromatin remodeling complexes."

Top: Blaine Bartholomew (standing) and lab technician Jim Persinger look at protein analysis results. Bottom: Doctoral student Bei Zhang prepares samples for DNA analysis.

DNA in motion

To understand what goes wrong with chromatin remodeling in cancer, researchers first must understand how remodeling normally works—in detail. Bartholomew has pioneered a way to follow the action.

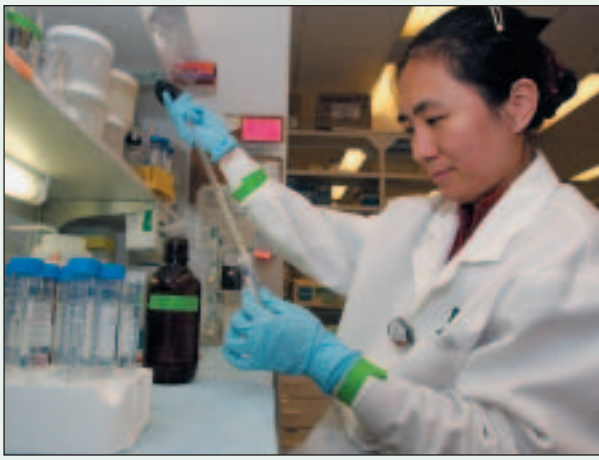
Into DNA, his research team inserts tiny molecular probes bearing radioactive tags. The probes are made from light-sensitive chemicals. When they're activated by a burst of light, a chemical reaction takes place and each probe transfers telltale radioactivity to any part of the remodeling complex that's touching the DNA in its vicinity.

The researchers expose the chromatin to a sequence of such light bursts, then separate out the protein and DNA segments for analysis. By identifying the radioactive bits, they can "map" the action that took place in a particular location. Doing this for multiple locations gives them a three-dimensional view of how remodeling complexes and DNA interact.

Bartholomew's team is using this labeling technique to study four chromatin remodeling complexes from yeast. After they have a good handle on how these complexes function normally, they'll make mutant versions of them to better understand what can go wrong.

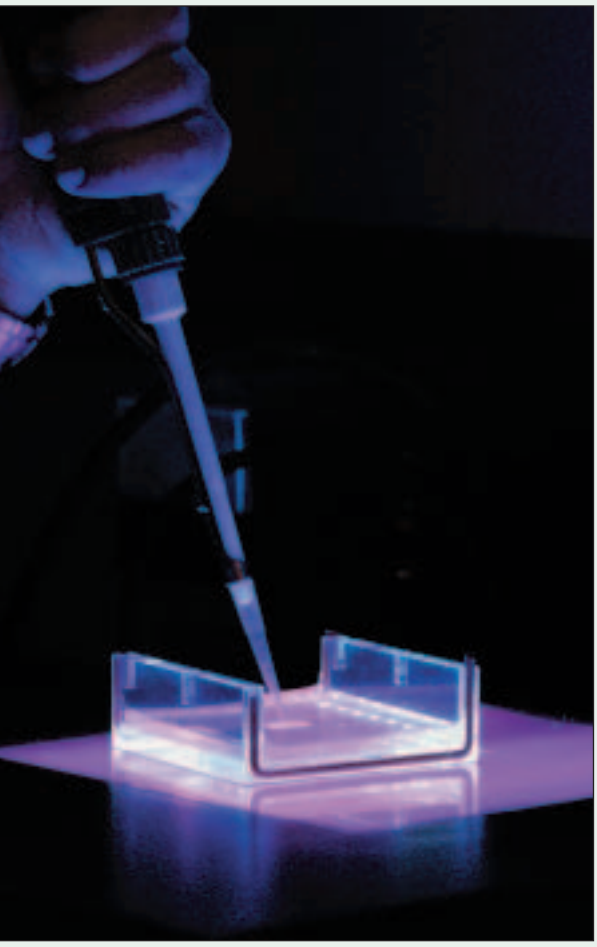
Why yeast, for heaven's sake? Actually, it's a model organism for this kind of work.

"Yeast are easy to manipulate genetically," says Bartholomew. "You can delete genes readily and look at the effects. And there's a lot of similarity at



"If you look at known cancers, you find that in many cases genes involved in remodeling complexes are mutated."

When there's a lot of damage to DNA, the cell's repair capacities falter. Repair mechanisms that are "error-prone" kick in.



▲ **By looking at a DNA sample under ultraviolet light, master's student Christian Coogan can isolate the DNA fragment he needs to create a new experimental strain of *E. coli*.**

the molecular level between yeast and humans."

In fact, chromatin remodeling complexes in yeast and humans are remarkably alike. Because they play such an important role in the cell, they've remained largely unchanged over hundreds of millions of years.

By using the chemical probes mentioned earlier, Bartholomew's lab group has pinned down some details about how a chromatin remodeling complex can activate transcription. It first "grabs" and loosens a short stretch of DNA at the top of the histone, then slides the DNA downward. "It creates this unusual DNA loop that moves [down] around the surface of the histone like a wave," Bartholomew says. On camera, this might resemble an elegant lasso trick. As DNA spools off the other end of the histone, the histone moves apart slightly from its nearest neighbor, leaving an open length of DNA between the two.

Turn off, tune out

Each cell's DNA contains the operating instructions for the entire body. But a given cell only needs certain genes switched on. A skin cell doesn't want genes that control kidney function to be active; it wants only the instructions from skin-related genes, and those only at the appropriate times.

As it happens, only one of the remodeling complexes Bartholomew is studying activates gene transcription. The other three *repress* transcription by condensing DNA. In short, some remodeling complexes unpack DNA, while others repack it and keep it put.

"Our data show that these two types of complexes—those that activate and those that repress—behave differently," Bartholomew says. "The one that activates transcription is much more disruptive to the chromatin. It does much more dramatic changing [of the DNA and histones].

"It's also not nearly as abundant in the cell. The other three complexes are 10 times as abundant."

That isn't so surprising, perhaps. "Usually whatever gets done in a cell is working against the pressures of repression," Bartholomew notes. "Most things are turned off most of the time. By and large, most things that can be expressed are not being expressed."

Typos in our DNA

Cellular processes aren't perfect, and mistakes can be made during DNA transcription. Because such genetic mutations often are the first step on the road to cancer, understanding more about them could help scientists find ways to prevent the disease. SIUC microbiologist Douglas Fix studies how ultraviolet radiation damages DNA and why a cell's machinery for fixing that damage sometimes fails, causing mutations.

DNA is composed of two strands—the famous double helix, which resembles a twisted ladder. The "rungs" of the ladder consist of pairs of four chemical bases represented by letters. T always pairs with A to make a rung; C always pairs with G. When it's time for the cell to reproduce, it must copy, or replicate, the exact sequence of bases—millions of them in every chromosome. Mutations are typos: mistakes in the sequence.

Different types of molecules absorb different wavelengths of light, and DNA happens to absorb UV light. "As a result, the bases in DNA can be excited by that energy and undergo chemical rearrangements," says Fix. UV light can cause two neighboring bases in a DNA strand to form an abnormal bond with each other. The abnormality is called a lesion, and it gums up the works when protein complexes in the cell try to replicate or transcribe the DNA.

Fortunately, cells can repair most lesions by stripping out the damaged bit of DNA and resynthesizing it. These repair mechanisms are typically "error-free," meaning that they accurately re-create the DNA.

But when there's a lot of damage, the cell's

repair capacity falters. Repair mechanisms that are "error-prone" kick in: they allow the cell to keep functioning, but at the price of mutations. They sometimes substitute a C for a T, or a G for an A.

Most mutations pose no problems. But some can trigger a cascade of cellular reactions that lead to cancer or other disorders.

By exposing cells to moderate doses of UV radiation, Fix can cause enough DNA damage to readily study DNA repair and mutations. For this work he's using a harmless laboratory strain of *E. coli* bacteria, a common choice for molecular biology experiments.

"We know exactly what kinds of mutations can occur in our strain of *E. coli,* and we know the genetic sequence," he says. "We also have access to other strains with varying capacities for DNA repair. We can analyze lots of samples very quickly and collect lots of data. It's much more difficult and much more expensive to do that with human cells, so we can cover more territory.

"Many of the mechanisms that repair DNA are fundamentally the same in bacteria and humans. By analyzing these fundamental processes in *E. coli,* we hope to relate them to things that happen in humans. We know that UV radiation mutates human cells, and there's good evidence to suggest that the same types of [lesions] that cause cancer in human cells cause mutations in *E. coli.*"

Fix recently was awarded a National Cancer Institute grant to correlate certain kinds of DNA lesions with certain kinds of mutations and to study their frequency. The grant, an Academic Research Enhancement Award, will allow several undergraduates to take part in the research.

By experimenting with different repair mechanisms, Fix and his students can trace a specific type of mutation back to the type of lesion that caused the trouble. They also can determine how often different types of UV-induced lesions occur (some are a hundred times more common than others) and roughly how often they tend to result in mutations. A given type of lesion may trigger mutations—may "foil" the cell's repair capacity—way out of proportion to its incidence.

Damaged by the light

"For all the years that UV light has been studied as a mutagen, it's been very difficult to make the kinds of correlations between damage and mutation that intuitively seem obvious," Fix says. "People have looked at damage distribution and compared that to mutation frequency, and found little correlation, in many cases."

That may be because scientists have overlooked a rare type of UV damage where neighboring T and A bases become bonded, he says. "Our pilot data suggest it plays an important role in mutagenesis even though it doesn't occur very often." His grant project will take a closer look at these T-A lesions and their role in causing mutations.

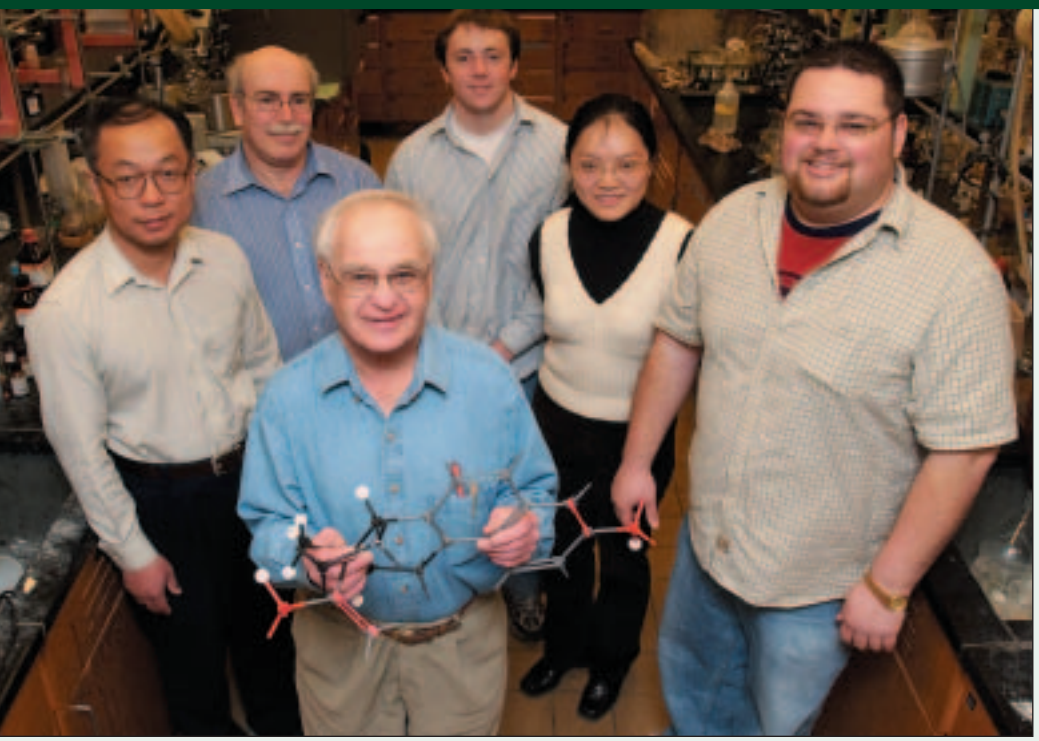
Fix's lab also will investigate an unexpected type of mutation that they've found sometimes results from C-T lesions, a much more common type of DNA damage. And they'll investigate another oddity they've discovered about UV-related mutations.

When the cell replicates its DNA, protein complexes must "zip open" the two strands of the DNA molecule to access them. For complicated reasons, there are differences in the way the two strands are copied. "We have preliminary data showing a fourfold difference in the frequency of particular mutations between the two strands," says Fix. He wants to know if this is a function of the cell's replication process or if UV damage occurs more often on one strand than the other—and if so, why.

Fix's work, like Blaine Bartholomew's, is basic rather than applied science.

"My research isn't going to cure cancer," Fix says, "but hopefully it will help someone else understand more about the process. Eventually the sum of knowledge can lead to applications that are very useful to all of us."

▲ Top: Master's student Carisa Anderson counts mutant bacterial colonies in a petri dish. Bottom: Doug Fix scans a DNA sequencing gel for mutated base-pair sequences.



▲ **Chemist Cal Meyers holds a model of the BDDA molecule, a potential anti-cancer agent. Behind him, from left: chemist Yuqing Hou; physiologist Stuart Adler; Joseph Stringer, a junior in chemistry; and Songwen Xie and Aaron McLean, doctoral students in chemistry. These researchers have worked to synthesize and modify BDDA and related compounds and to understand how they function in the body.**

The estrogen connection

Basic research can sometimes lead directly to applications, however. At SIUC, interdisciplinary work that began with fundamental research in chemistry has produced what may be a useful new treatment for prostate cancer. A group of scientists from chemistry, physiology, animal science, and food and nutrition are studying how estrogen-like compounds may contribute to cancer—or be used to treat cancer.

An estrogen is any chemical compound with estrogenic (feminizing) effects. The estrogen produced in the human body is estradiol, a steroid hormone. Women, of course, need estradiol to lead healthy lives and bear children. Men need it, too: for example, men must convert testosterone to estradiol in order to build bone tissue.

On the down side, some cancers, such as some types of breast cancer, are fueled by estradiol; they're said to be estrogen-responsive. And the estrogens in birth control pills or hormone replacement therapy carry risks for some women.

The SIUC group may have found a way to dismantle this double-edged sword—to separate useful estrogenic effects from unwanted or harmful effects. Like so many scientific advances, this one was unplanned.

Cal Meyers, professor emeritus of chemistry and director of the Meyers Institute for Interdisciplinary Research in Organic and Medicinal Chemistry, picks up the story. "We were treating estradiol with carbon tetrachloride—just doing basic research on electron transfer during fundamental chemical-reaction studies," he says.

"When we did this we found that the ring structure [characteristic of steroids] opened up, so that the compound was no longer a steroid. We had the compound tested and found that it was very estrogenic."

By this simple chemical reaction, Meyers' lab had created a nonsteroidal, estrogen-like compound. Its name is such a mouthful—bisdehydrodoisynolic acid—that they simply call it BDDA. Meyers and several colleagues—chemist Yuqing Hou, reproductive physiologist Todd Winters, nutrition physiologist Bill Banz, molecular biologist Stuart Adler, and biochemist Walter Dandliker (all but the latter are with SIUC)—have patented the use of BDDA as a potential treatment for prostate cancer and other medical conditions.

Estradiol and other estrogenic compounds once were used to treat prostate cancer, because they shrink prostate tissue and blunt testosterone production. Unfortunately, they also shrink the testes, causing impotence and sterility; they have other feminizing side effects, such as breast enlargement; and they promote blood clots. But BDDA may change all that.

A plus for prostate cancer

BDDA, like many organic compounds, exists in two forms: a "right-handed" structure and a "left-handed" structure that are chemically identical mirror images of each other. They're referred to as the plus (+) and minus (-) structures, respectively. Meyers and Hou knew that these two forms of BDDA might have different effects on the body. So they convinced Winters, Banz, and veterinarian Nancy Henry—all with SIUC's Dept. of Animal Science, Food and Nutrition—to test them in lab animals.

Meyers initially patented BDDA as a weight loss agent, since the compound was found to promote weight loss in female mice rather than the weight gain associated with many estrogens. But Winters, Banz, and Henry also discovered another intriguing effect of BDDA. Testing it in normal male rats, they found that both forms of the compound shrank prostate tissue—but that the right-handed version, (+)-BDDA, did it with almost no shrinking of the testes or other feminizing side effects.

This finding raised the intriguing possibility

that (+)-BDDA might be used to treat prostate enlargement or even prostate cancer. The team went on to determine that oral preparations of this compound, not just injected preparations, were effective—a key selling point for eventual studies in humans.

Working with cell cultures, Henry found that (+)-BDDA inhibits the growth of human prostate cancer cells. "The effect is statistically significant and consistent," she says.

At that point the team asked Dennis Lubahn, a physiologist at the University of Missouri, Columbia, to test (+)-BDDA on a special strain of transgenic mice that spontaneously develop prostate cancer. If the compound keeps the cancer in check in these animals, the SIUC team hopes that a pharmaceutical company will step in to fund stage-1 clinical trials in humans.

Designer drugs

The work with BDDA opens up the possibility of making other "designer" estrogens. Songwen Xie, a doctoral student working with Meyers, has developed "a battery of compounds that may be as good as or better than BDDA," Winters says.

Designer estrogens might be developed to treat some types of breast or uterine cancer, or to fine-tune birth control or hormone replacement therapy so these drugs have fewer undesirable side effects.

"It looks like the whole package [of estrogenic effects] is separable," says Stuart Adler, an associate professor of physiology who also is part of the team. "We may be able to pick and choose the effects we want."

Hormones like estradiol bind to proteins called receptors. In the case of estradiol, the receptors are located in the nucleus of the cell. After binding takes place, the hormone/receptor complex interacts with various proteins in the nucleus to change gene expression and produce hormonal effects.

"We used to think of this [binding] with receptors as being like a lock and key," says Adler. "If they were the right shape, compounds would fit into the receptor and open the lock. But we now know there are subtle shape differences among compounds that can activate the estrogen receptor."

As it turns out, the "lock" can be opened to varying degrees. Consequently, some compounds that fit the receptor rather poorly—that open it just partway—can still produce substantial estrogenic effects.

Just as surprising, some compounds produce estrogenic effects in some tissues and *anti*-estrogenic effects in other tissues. For example, the cancer drug Tamoxifen normally blocks estradiol's effects in the breast, but it acts like estradiol on the uterus. (Thus breast cancer patients on Tamoxifen must be closely monitored for uterine cancer.)

These selective effects gave rise to a new term: SERM, for selective estrogen receptor modulator. Tamoxifen was the first known SERM compound; Meyers and Adler think that BDDA may be another. BDDA "hardly binds at all" to the estradiol receptor, says Meyers—yet it has strong estrogenic effects. And like Tamoxifen, it produces only some of estradiol's effects.

This selectivity, which holds so much promise for medical applications, poses difficulties for cancer-related environmental research. Many industrial chemicals that are widespread in the environment can interact with estrogen receptors. Scientists want to know what potential health risks, including cancer risks, are posed by these so-called "environmental estrogens."

Because environmental estrogens may act as SERMs, toxicology testing of these compounds must be more comprehensive than scientists might have anticipated, Adler says. For example, you can't just look at effects in one type of tissue, because a SERM can be benign in some tissues but carcinogenic in others. Adler thinks that BDDA offers "a perfect model system" for exploring some of these complexities.

One type of "designer" estrogen patented by SIUC researchers may be useful against prostate cancer.

Oddly enough, phytoestrogens—estrogenic compounds produced by plants—may provide some defense against environmental estrogens. Winters, Banz, and Henry have studied the physiological effects of soy phytoestrogens (there are several different types of these compounds), including effects on reproductive tissue.

The promise of soy

Where cancer is concerned, they say, the soy story is promising, but complicated. Estrogenic soy compounds have different effects in different types of tissues and can actually make matters worse in the case of certain cancers. For example, some labs have found evidence that low doses of genistein, one of the soy phytoestrogens, can stimulate some types of breast cancer cells.

On the other hand, soy seems to have protective effects if consumed early on and regularly. People living in Asia, where high-soy diets are common, have much lower rates of prostate and breast cancer than U.S. residents do. By keeping some of the body's estrogen receptors occupied, soy phytoestrogens may be able to keep environmental estrogens from binding and having pernicious effects.

Henry notes that many animal studies indicate that soy offers protection against the risk of cancer from environmental estrogens. This protective effect isn't due

Ginseng and Cancer: A Follow-Up

In spring 2001, *Perspectives* visited the lab of physiologist Laura Murphy to report on cancer research involving ginseng. Three years later, that work still looks promising.

Murphy and her students had found that a water extract of American ginseng slowed down the growth of human breast and prostate cancer cells in culture. They also had discovered that female mice injected with human breast cancer cells develop much smaller tumors if their drinking water is laced with ginseng. (Because these mice are immunosuppressed, they can't fight off the cancer themselves.)

Since then, Murphy's lab has tested the effects of ginseng on breast cancer cells resistant to chemotherapy drugs, including hormone therapies like Tamoxifen. "Cancer in general is pretty bad about developing resistance [to drug therapy]," says Murphy. "Cancer cells develop resistance to different drugs through different means, but regardless of the mechanism, we're able to inhibit proliferation of these cells with ginseng."

A $150,000 grant from the Penny Severns Breast and Cervical Cancer Fund through the Illinois Department of Public Health is funding these studies. And a new, $300,000 National Cancer Institute grant will allow Murphy to study the effect on cancer cell cultures of ginseng co-administered with various chemotherapy drugs. In early experiments, she has found "much greater inhibition of cell growth" with the combination than with either compound alone.

She's already begun following up those findings with animal studies.

"We've given subtherapeutic doses of ginseng and of cancer drugs to immunosuppressed mice that we inoculated with human breast cancer cells," she says. "Individually, these are doses at which we would not expect to see a therapeutic response. But when you give them together, it seems to prevent the cancer from growing."

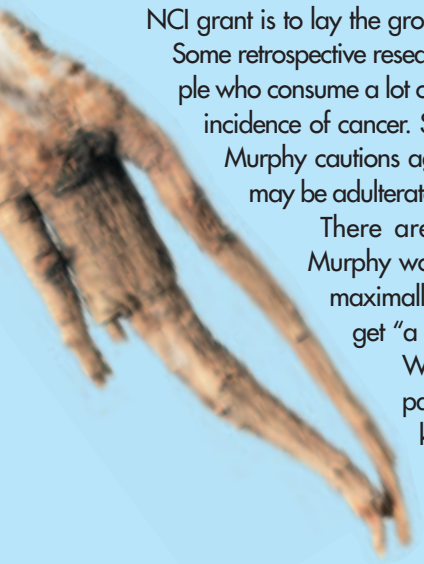
These animal studies are treating cancer at a very early stage, although the cells themselves are from advanced metastatic human cancers. "We want to look at full-blown cancer in the near future," Murphy says. The goal of the NCI grant is to lay the groundwork for studies in humans.

Some retrospective research studies, most done in Korea, indicate that people who consume a lot of ginseng as part of their normal diet have a lower incidence of cancer. Such dietary consumption appears to be safe. But Murphy cautions against people self-dosing with supplements, which may be adulterated or ineffective and can interfere with other drugs.

There are some 20-25 active compounds in ginseng. Murphy would like to test all of them, determine which ones maximally inhibit cancer cell growth, and combine them to get "a potent anti-cancer cocktail."

Will ginseng fulfill its promise for human cancer patients? Much work remains before the answer is known. Murphy is optimistic, however.

"This is some really exciting stuff," she says.



solely to phytoestrogens, however; soy protein plays a role as well. Consumers should get their soy by eating foods like tofu, says Banz, not by taking supplements.

In a major three-year project, Winters, Banz, Henry, and Adler also are investigating the synergistic effects of soy phytoestrogens and certain vitamins on prostate cancer. The study is supported by a $429,148 grant through the Illinois Attorney General's Office from a vitamin antitrust settlement fund. "Other scientists have looked at phytoestrogens and vitamins separately," says Henry, "but putting them together is where we're getting great results."

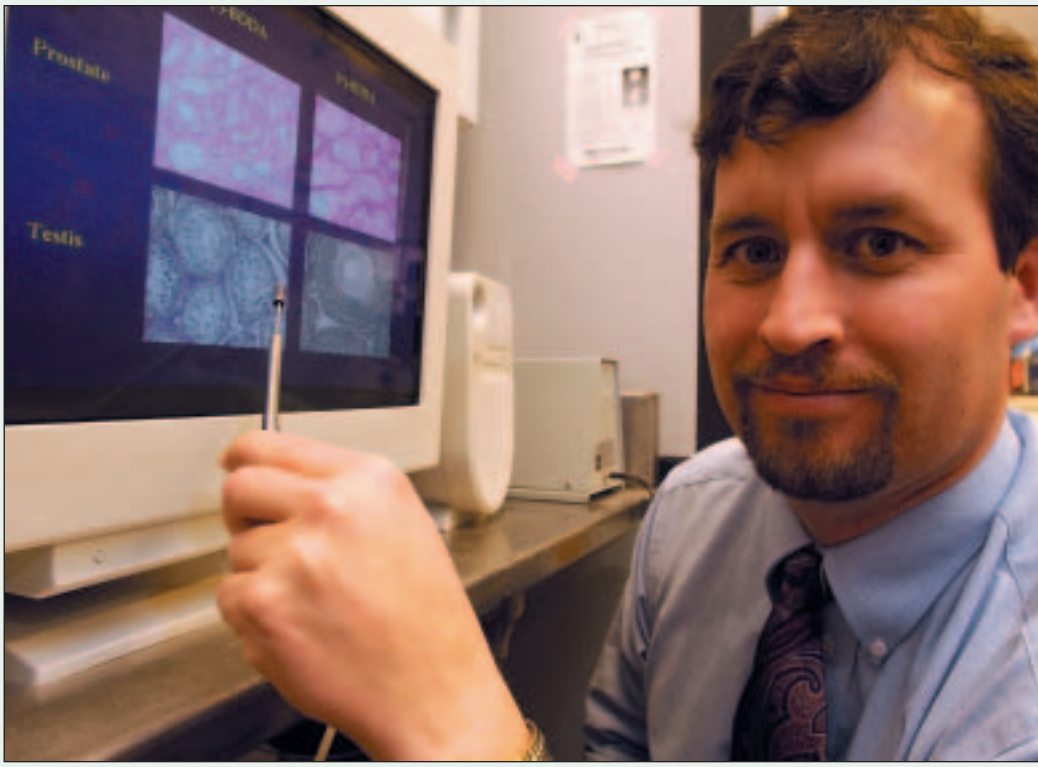
The researchers fed one group of normal male rats a soy-free diet, a second group a low-phytoestrogen soy diet, and a third group a high-phytoestrogen soy diet. Within those three groups, some of the rats received a high dose of vitamin A, some received vitamin D, some received vitamin E, and some received no extra vitamins. After eight weeks, the team found that the diet combining vitamin E with a high level of soy phytoestrogens had a pronounced effect in shrinking the size of the prostate.

Henry then tested combinations of vitamins and various soy phytoestrogens on human prostate cancer cells. "Vitamins E and D in combination with each other and with soy phytoestrogens basically stop growth of prostate cancer cells [in culture]," she says. "We're excited about these results."

Of the phytoestrogens, genistein seems to have the most significant effects. The team now plans to implant human prostate cancer cells into immunosuppressed mice and see if the vitamin/soy combinations can hold the cancer cells in check or kill them.

Meanwhile, Adler is studying what happens when soy phytoestrogens bind to estrogen receptors. Scientists have found that two protein families in the nucleus act as modulators for estrogenic compounds. One family helps the compounds activate estrogen receptors; the other family has the opposite effect. These critical modulators vary across cell types, which may account for some of the selective effects SERMs have.

▲ Top: Todd Winters shows the different effects that the two forms of BDDA have on prostate and testis tissue in rats. ▶ Middle: Nancy Henry (right) and Monica Zaworski, a senior in animal science, have tested BDDA, soy phytoestrogens, and vitamins on human cancer cells. ▼ Bottom: Bill Banz (left) and his students (here, undergraduate Ben Wooley) have tested BDDA and phytoestrogens in lab animals.



Adler has shown that at least one soy phytoestrogen, genistein, can change the levels of the modulators, making the cell less responsive to it and to other environmental estrogens. By doing so, genistein is telling the body, in effect, "We're not really estradiol, even though we look similar." This adaptation may prevent health problems by neutralizing what would otherwise amount to an increase in estrogen load.

With funding from the National Institutes of Health, Adler is investigating the molecular mechanisms and gene sequences that allow genistein and other SERMs to influence modulator levels. "If we can understand the different classes of modulators, we might be able to make cancer cells more responsive to therapy," he says.

Returning to the designer drug concept, he raises the possibility of tailoring cancer therapy by combining compounds that block certain effects with compounds that promote other effects.

"It's not just a pipe dream to think that we can do this," he says. "The goal is to go from the bench to the bedside. It's still a big step to get to clinical trials, but ultimately we want to be helping people."

Adds Meyers, "That's why interdisciplinary research is so important.

"We've got work to do." ✚

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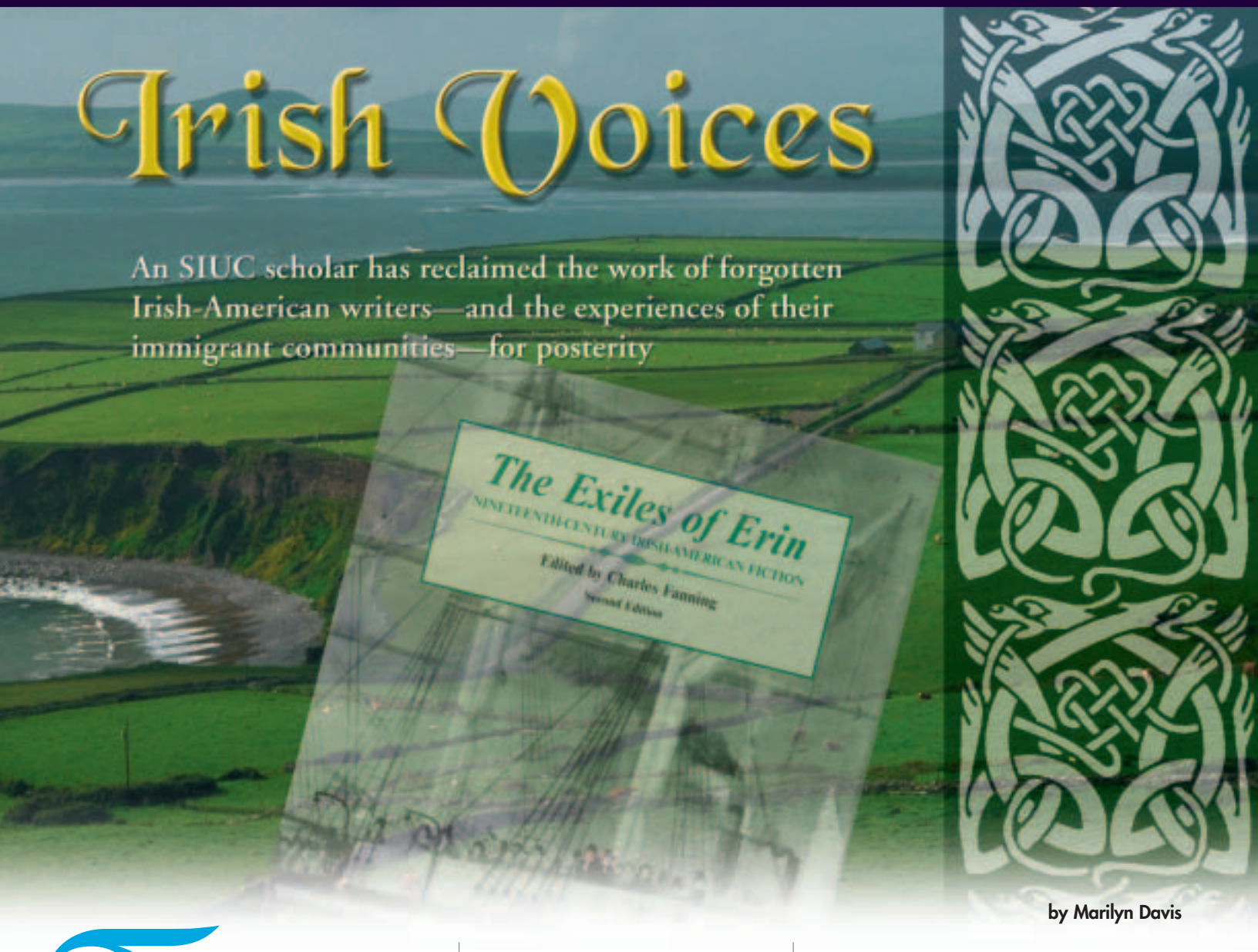
Irish Voices

An SIUC scholar has reclaimed the work of forgotten Irish-American writers—and the experiences of their immigrant communities—for posterity



by Marilyn Davis

The Irish who came by the millions to U.S. cities in the 1800s faced prejudices that dismissed them as drinkers, brawlers, and illiterate liars. They were called uncivilized and subhuman. Their religion (most were Catholic) was often viewed with hostility. They endured grinding poverty in inner-city tenements, did backbreaking labor, and encountered discrimination in jobs and housing.

"They were pioneers of the American ghetto," says Charles Fanning, a professor of English and history at SIUC.

From this rough beginning came countless success stories and one of this nation's great ethnic heritages. (More than 40 million Americans today claim some Irish ancestry.) From it also came a distinctive literary voice that tells us a great deal about our shared history.

It's thanks to Fanning—widely seen by literature and history scholars as the dean of Irish-American studies—that so much is known about this voice. Until he began his research, in the early 1970s, most Irish-American writing prior to 1900 had been forgotten, overlooked on library shelves and hidden away in dusty newspaper and periodical archives.

Focusing mostly on fiction, Fanning has excavated this literature and reintroduced it to the world. Three of his books have won national awards, and this year SIUC has recognized his achievement with the Outstanding Scholar award.

Fanning, who is half Irish, grew up in the "very Irish" small town of Norwood, Mass., now a suburb of Boston. (He remembers, as a child, hearing Irish spoken on the streets by immigrants from Galway, though he never learned the language himself.) He went to Harvard for his bachelor's degree and a master of arts in teaching, then earned an interdisciplinary doctorate in American civilization from the University of Pennsylvania, focusing on literature, history, and art.

For his dissertation he wanted to treat an Irish-American topic, in part to learn more

about his own heritage. "I've always been interested in how literature helps us clarify history, and vice versa," he says. He found an ideal subject in a Chicago bar.

Mr. Dooley, a fictional Irish-American bartender with humorous opinions on politics and life, was the creation of Irish-American journalist Finley Peter Dunne. In the late 1890s Dunne gained national fame with his syndicated newspaper columns written in Dooley's persona. But Dunne's pre-syndication columns, published in the Chicago *Evening Post*, were the ones that intrigued Fanning.

In these earlier, grittier columns, full of social commentary and political satire, Mr. Dooley told the stories of his Irish neighbors on Chicago's near South Side. Fanning's digging uncovered 300 of these pieces that had never been collected. Together, he says, they give "as full a picture as you're ever going to get of what it was like to be a working-class Irish immigrant in an American city in the 19th century."

The columns became the focus of his doctoral dissertation and, in 1978, of his first book. *Finley Peter Dunne and Mr. Dooley: The Chicago Years* netted Fanning the 1979 Frederick Jackson Turner Award from the Organization of American Historians. In 1987, he grouped many of the columns by theme and republished them with commentary as *Mr. Dooley and the Chicago Irish: The Autobiography of a Nineteenth-Century Ethnic Group.*

"Dunne is the first Irish-American voice of genius," says Fanning. "He thinks enough of these people—factory workers, laborers—to dignify their lives and to turn them into real literature. And he does it in an Irish brogue."

When other 19th-century writers wrote dialogue in brogue, it was to mock the Irish. Dunne turns that notion on its head, Fanning explains: "He does for the Irish-American voice what Mark Twain does when he lets Huck Finn tell his own story [in his own dialect]: he legitimizes it. The best of Dunne's pieces are eloquent and beautiful."

In the 1980s, Fanning broadened his research to the entirety of Irish-American literature in the 19th century. Searching out other lost and neglected writers, he combed the card catalogs and shelves of the nation's best archives, including Harvard's Widener Library, the Library of Congress, the New York Public Library, and the Newberry Library in Chicago.

To fund his work, he won fellowships and grants from a veritable "Who's Who" of agencies and organizations that support humanities research: the National Endowment for the Humanities, the Rockefeller Foundation, the American Council of Learned Societies, the American Antiquarian Society, and others.

Fanning's discoveries illustrate the profound interconnectedness of history, culture, and literature. Before the 1840s, Irish immigrants came to America by choice. Although they faced prejudice, they were well educated and well adjusted to life in the States.

"That early stage of writing has lots of satire and parody," says Fanning. "The early generations of immigrants were confident enough to laugh at themselves, at the view that other Americans held of them, and at America."

But this sophisticated comic fiction did not last. As Fanning writes, "All such laughter stopped" with the Great Hunger—the years of famine in Ireland resulting from the potato blights of 1845. More than a million people died; some million and a half emigrated to the United States between 1845 and 1855. These "involuntary" rural immigrants came to America's cities to escape starvation, only to suffer widespread poverty and disease.

Earlier Irish-Americans had written for the general public, but "Famine Generation" writers wrote for other immigrants. They produced "rags-to-riches" stories; romantic novels thick with nostalgia for the home country; and, above all, moralizing books showing readers how to get along in America and warning them not to be tempted away from Catholicism.

Most of this fiction had unlikely plots and sentimentalized characters, but it was realistic in one respect: setting. "This literature tells you what the inside of a tenement flat looked like and how people lived day to day," says Fanning. "Even in the didactic stuff you get a vivid depiction of daily life and working conditions. You also get plenty of illustrations of anti-Catholic prejudice" faced by Irish-Americans. Literature, he says, makes these issues "concrete."

Fanning collected many of the shorter pieces he "reclaimed" in *The Exiles of Erin: Nineteenth-Century Irish-American Fiction* (1987), which won the American Book Award from the Before Columbus Foundation for outstanding contribution to American literature.

As the 1800s came to a close, writers treating Irish-American themes, like Dunne, began to publish realistic fiction once again geared to general readers. But the Irish-American voice fell silent in the early 1900s, Fanning discovered. Thanks to anti-immigrant sentiment and the turmoil of World War I (which put anti-British Irish nationalists in America in an awkward political position), not many writers wanted to call attention to their ethnicity. After legislation in the early 1920s that restricted immigration, there were few Irish newcomers. And as the Irish-American middle class grew, it focused on assimilation.

Fanning calls this a period of "cultural amnesia." The next great writer to treat Irish-American themes, James T. Farrell, essentially had to reinvent Irish-American literature from scratch in the 1930s, he says.

Farrell began his career with the *Studs Lonigan* trilogy, his most famous novels, and followed up with dozens of other books, all centered in a mostly Irish

"This literature tells you what the inside of a tenement flat looked like and how people lived day to day."

–Charles Fanning

working- and middle-class enclave on Chicago's South Side in the first half of the 20th century. "Farrell does for the South Side of Chicago what William Faulkner does for that little county in Mississippi and what [James] Joyce does for Dublin," says Fanning. "He makes it universal."

Fanning collected some of Farrell's shorter pieces in *Chicago Stories of James T. Farrell* and is organizing a celebration of his work at the Newberry Library this year, the 100th anniversary of his birth. Since *Studs Lonigan*, he says, Irish-American fiction has blossomed, and it still centers on urban life. Two of Fanning's favorite contemporary writers are William Kennedy, whose best-known novel, *Ironweed,* is one of a cycle of Irish-themed novels set in Albany, and Alice McDermott, whose novel *Charming Billy,* set in New York City, won the National Book Award in 1998.

The common thread in 20th-century Irish-American literature, Fanning says, is "the idea of community fostered by a specific place. Irish-American writers have [their universe] in the city neighborhood—it's enough of a canvas for them to do their work."

Fanning's own masterwork is *The Irish Voice in America,* which covers the entire scope of Irish-American fiction. Published in 1990, with an expanded second edition in 1999, it won the American Conference for Irish Studies' Prize for Literary Criticism, and historian Lawrence McCaffrey says it established Fanning as "the leading Irish-American studies scholar."

Fanning came to SIUC in 1993 to build an interdisciplinary program in Irish and Irish immigration studies drawing on strengths in several departments and on the top-notch Irish literature holdings at Morris Library's Special Collections. With the help of a $240,000 grant he received in 1995 from the U.S. Department of Education, the new program has hosted international conferences, developed new courses and online resources (see www.siu.edu/~ireland), and funded scores of faculty and student exchanges with the National University of Ireland, Galway.

Fanning, who has written, co-written, or edited 12 books, has two more irons in the fire right now. One is a wide-ranging memoir about his own upbringing and ancestors, which he is enjoying greatly.

"It's very freeing," he says of this type of writing, which will look at history through the prism of his family and home town.

He's also writing and gathering illustrations for a book on Irish-American culture during the Great Depression. "I'm discovering that there was a tremendous flowering of Irish-American art in the 1930s," he says. "I'm looking at writers, artists, radio-comedy people, comic-strip creators. It's kind of a renaissance, and no one has really put it all together."

Recent years have seen a resurgence of interest in Irish music and dance. Now the work done by Fanning and the students following his lead is opening other new avenues to explore the vibrant Irish-American past.

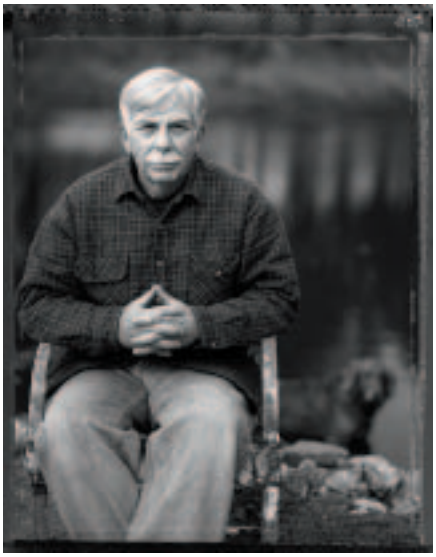
For more information, contact Dr. Charles Fanning, Dept. of English, celtic42@siu.edu.

Peerless Portraiture

▲ "Ross," by Andrea Behrends. 2003.

▲ "Marge," by Josh Sanseri. 2003.

▲ "Herin," by Polly Chandler. 2003.



▲ "Dad," by Nicole Isaacson. 2003.

It was nearly a sweep: graduate and undergraduate students of SIUC documentary photographer Dan Overturf dominated two of the three college/university award categories in the Photo Imaging Education Association's 2004 photography competition.

For the second year in a row, the grand prize in the portfolio category went to M.F.A. student Josh Sanseri, whose graduate thesis show will focus on owners of small businesses. M.F.A. student Polly Chandler took first prize in this category, and Nicole Isaacson took third. Grand prize in the single-image category went to Andrea Behrends; Ann Dodge took second prize; and Ed Frey III took third.

SIUC photography students have landed a grand prize in the PIEA competition for seven consecutive years—ever since they began entering. Prize-winning photographs are exhibited at the PIEA's annual convention and in venues around the country and are posted online (see www.piapma.org).

—Marilyn Davis

▲ "Buddy," by Ann Dodge. 2003.