FINAL

THE SUN

Saturday, January 8, 2005 Baltimore, Maryland F 50 cents

Young researcher stalks cancer

Research: With little life outside the lab, a Hopkins worker studies a chemical that shuts down tumors in rats.

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SUN STAFF

Clutching a clear plastic tub containing two enormous white rats, Young Hee Ko scampers through a labyrinth of laboratory hallways at the Johns Hopkins Institute for Basic Biomedical Sciences.

Down stairwells, through automatic doors and across glassed-in bridges spanning busy East Baltimore streets, she is a blur of black clogs, blue jeans and obligatory white lab coat.

Ko and her pink-eyed rats, named "One Dottie" and "July Mom" (JM), are late for a date in Dr. Martin G. Pomper's radiology lab, a pit stop in their marathon race to find a cure for cancer.

Trailing her are Ko's colleague and mentor, biochemist Peter Pedersen, and David Rini, a medical illustrator and their project manager. They are assisting with her investigation of a compound called 3-bromopyruvate, otherwise known as 3-Bp.

Cheap and easy to produce, 3-Bp has snuffed out large, aggressive liver cancers in rats by blocking the tumors' ability to metabolize the glucose they need to survive.

In a small study published last month in *Biochemical and Biophysi-* [*See Ko, 6A*]

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Young Hee Ko prepares One Dottie (the rat she's touching) and July Mom for PET scans of their cancerous tumors, which she is treating with a commonly available chemical.

Little sleep, long hours in lab

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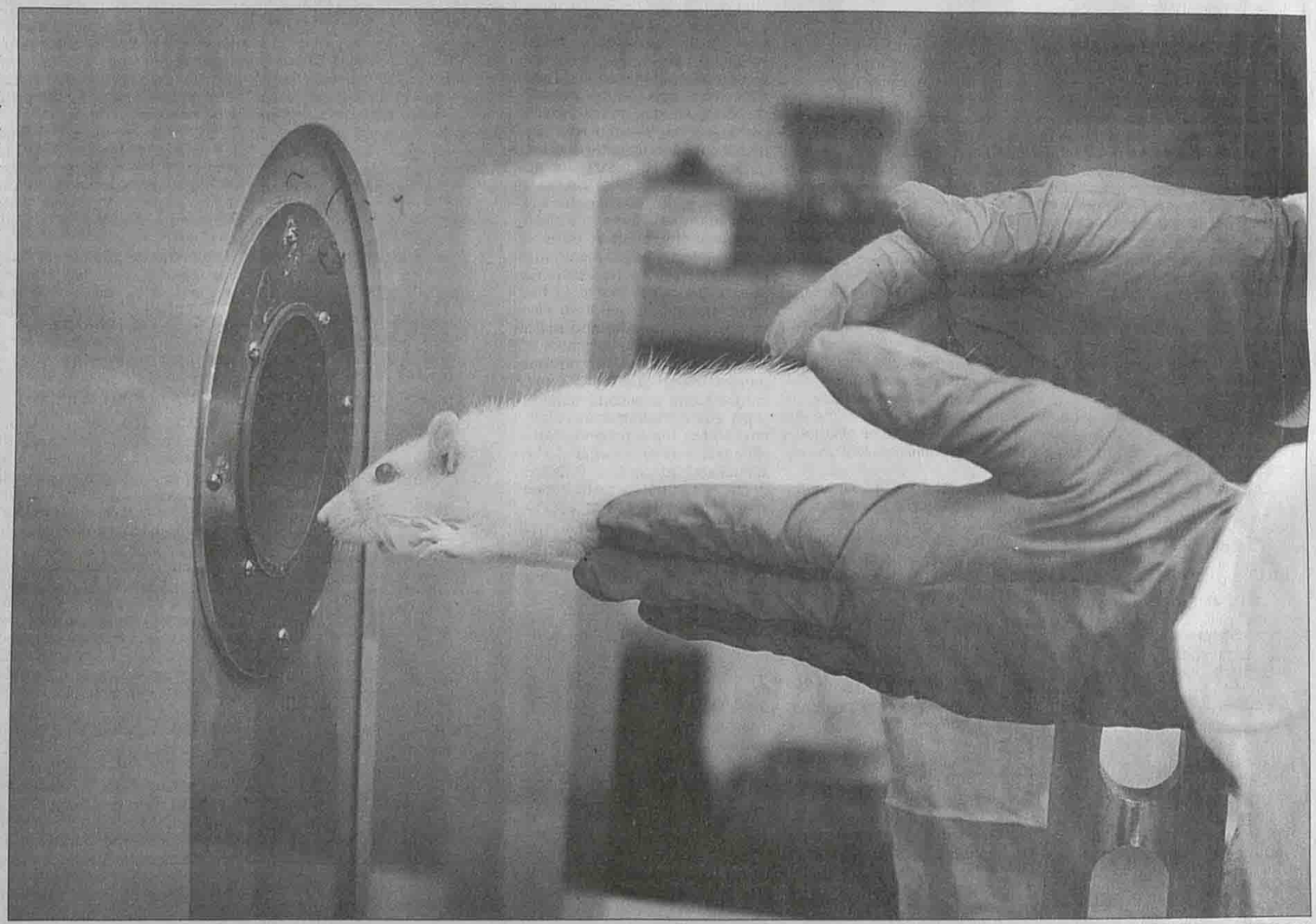
cal Research Communications, Ko and Pedersen reported those findings. They reported that 3-Bp did not appear to harm healthy tissue and that there was no recurrence of the disease — and no exceptions. All the rats recovered.

It's not a victory in the war on cancer, not by a long shot. Researchers have seen too many chemicals that destroyed tumors in rodents but ultimately failed in humans. Even if they find that 3-Bp works on people, too, the researchers know how hard it is to get funding for full clinical trials — especially for a cheap, common chemical that can't be patented.

But Ko, her colleagues and her rats are a fascinating story of science in progress, one that plays out every day in laboratories around the country as researchers spend years, or entire careers, pursuing ideas that could turn into medical breakthroughs — but can just as well turn into dead ends.

For now, Ko's team believes it has good reason for hope — and for Ko herself, even more reason to put in the obsessive, 18-hour days and sleepless nights that have ruled the very private scientist's life for more than a decade.

So far, they say, 3-Bp has also worked well against human liver and breast cancer cell lines tested *in vitro*, in the lab. Compared with other agents that cured cancer in rats but not in humans, Rini says, 3-Bp works at "a much more fundamental level of cell metabolism. You could say the more basic you go, the more we have in common with rats."



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One Dottie is carefully inserted into the PET scanner at the Johns Hopkins Hospital radiology lab. She is so big it cannot properly scan her malignant tumor.

Impressive results

There's no doubt that Ko's results have impressed some veteran researchers. "I've been in cancer study for 20 years, and I've never seen anything like this, that just melts [tumors] away," Pomper says.

Dr. David M. Hockenbery of the Fred Hutchinson Cancer Research Center in Seattle said Ko's team still needs to show whether 3-Bp works on other types of cancer. But the results so far, he says, look "quite dramatic and quite impressive."

"It's unusual to see this complete a response in tumor models like this," he says. And while other drugs have "cured" liver cancer cell lines, he says, the drugs themselves are highly toxic. The rats Ko treated with 3-Bp "looked quite healthy."

Donald S. Coffey, director of research at the Brady Urological Institute at Hopkins — like Hockenbery, unaffiliated with the Ko study — says 3-Bp "blocks one of the most basic and common pathways unique to cancer cells, and that is the burning of sugar."

The facts that 3-Bp has also been nontoxic to the animals and appears to produce cures and long-term survival add up to "a dramatic discovery," he says. Now, "I'd like to see [the treatment] generalized to other tumors."

The researchers know they have a long way to go. "We're all very realistic, all pretty guarded and happy to take it to the next step before we all get too excited," Rini says. Their next target, they say, is breast cancer.

'Beautiful' lab rats

In Pomper's radiology lab, Ko's rodents lie wide-eyed and motionless, sandwiched between absorbent paper blankets. Worried that they're too heavily sedated, Ko speaks to them, strokes and squeezes the animals to keep them breathing. She moistens their eyes with drops.

The Korean-born scientist confesses that she didn't like working with rats at first, but "now, I see them as the most beautiful animals you can ever imagine.

"So, I love them. I go in there much and I talk to them, I take care of them, I give them everything they need. These are my babies."

They are no ordinary lab rats. They're two of the biggest, fattest lab rats anybody in the room has ever seen. One Dottie weighs well over a pound — about the size of a kitten. In fact, she might actually be too fat to fit into the tube of the positron emission tomography (PET) scanner, which is why everyone is gathered here today.

But more important, One Dottie and JM have breast cancer — spontaneous, grape-sized tumors that make them ideal candidates for testing 3-Bp's effectiveness against a second form of malignancy.

James Fox, a radiology technician, centers One Dottie on his lab bench and injects glucose laced with a radioactive marker into a vein in One Dottie's tail. He waits 20 minutes, then tapes the corpulent rodent to the little table that will slide her into the soda-can-sized opening of the PET machine.

Aggressive cancers consume prodigious amounts of glucose. If this test works, the radioactive marker in the glucose will crowd into the cancer cells. The positrons it emits from there will cause the cancers to glow on a nearby computer screen.

It's one of the best diagnostic tools doctors have for spotting these kinds of tumors. If the tumors stop glowing after treatment, it means they've stopped using glucose. They're dead.

But for today, Ko just wants Pomper's help to determine whether the rats' breast cancers are aggressive enough to show up in a PET scan.

So Fox squeezes One Dottie gently into the scanner, but her tumor presses against the chamber wall — not ideal for a good image. JM fits nicely, however; soon her breast cancer is glowing brightly on the monitor.

"This is great. This is great," Fox says.

Work with worms

Ko first worked with 3-Bp 15 years ago as a graduate student at the University of Washington. Back then, she was searching for a substance that would block a vital enzyme in nematodes — tiny roundworms that have a long history as agricultural pests.

3-Bp plugged into what Ko describes as the "business end" of that nematodal enzyme, rendering it permanently inactive — like inserting a key and locking it up. Once exposed, the nematodes were finished.

Like more than a few promising ideas, however, the agricultural future of 3-Bp evaporated when Ko's professor at UW couldn't get funding for further research.

Arriving at Hopkins in 1991 with a doctorate in biochemistry and biophysics, Ko began working in cystic fibrosis research, but she eventually switched almost full time to cancer.

Seven days a week

"She has never taken a vacation," Pedersen says. "She works seven days a week. She comes in at 6 or 7 o'clock in the morning ... and goes home sometimes after midnight. If you want verification of that, you can just ask the guards."

Petite and bespectacled, Ko guards her privacy. She won't disclose her age or speak much about her childhood in Seoul, South Korea, before arriving in the United States to study in 1982.

She concedes that, except for a recently purchased Baltimore County townhouse, a beloved 4-year-old nephew and other family members she lives with, she has almost no life beyond her science, her lab and her rats. She rarely sleeps more than two hours a night.

"This is my life," she says. "I give up everything."

But it's plenty, she insists: "When you try to study science there are so many areas that you have never seen, it's just like traveling. Every field, every aspect, every topic you touch is giving you more excitement. ... Every time I discover a little thing, I get so excited I jump all over."

When Ko turned her attention to cancer, she began looking for a way to destroy the cellular "power plants" that fuel the most aggressive tumors. Pedersen, who has studied cancer cell metabolism for decades, was an ideal mentor, although he describes himself as "mainly a bystander and a technician" in

Ko's research.

He says German scientists discovered in the 1920s that aggressive cancers have huge appetites for glucose, which they break down to extract energy before excreting the waste products — lactate and pyruvate — through specialized "gates" in the cell wall.

This appetite for glucose, Pedersen says, presents cancer-fighters with an enticing target — a potential Achilles' heel. And Ko's investigation, funded by the National Cancer Institute and the Hopkins Department of Radiology, was designed to find compounds that might choke off this high glucose metabolism.

Drawing on her old agricultural research, Ko added 3-Bp to her list of candidates because it closely resembles the cancer waste product pyruvate. Ko believed that chemical similarity might allow 3-Bp to slip into the cancer cells like a Trojan horse, through the same gates used to eject natural pyruvate. On the other hand, she was worried that 3-Bp would also kill normal, healthy cells.

"If you want to know the truth," Pedersen says, "I never knew she was even trying this thing. When she did, I told her it would never work."

Especially not with these rats. Many had induced liver cancers so large the animals were near death. On a human scale, some of those tumors would be the size of cantaloupes.

Few researchers attack such advanced cancers, yet "those are the ones you really want to cure, because people are close to death," Pederson says.

Despite her mentor's misgivings, Ko went ahead, using 3-Bp to treat 19 of 33 rats with liver cancers. The injections — directly into the tumors or, in some cases, into the rats' abdominal cavities — continued for five days. But energy production in the cancers shut down within minutes.

In weeks, as their tumors dwindled or dried up, all 19 previously sick and lethargic rats regained their energy, Pedersen says: "They were really more active than they were beforehand. They were enjoying life again."

PET images confirmed it: The tumors glowing so brightly in the pre-treatment images had turned dark. And somehow, healthy tissues were unaffected. All the rats had been cured of their cancers for less than $5 worth of a chemical that's already on the shelves of laboratory supply houses.

"Unless I had seen it, I would never believe it," Pederson says.

Skeptical silence

Word of their results generated what Ko and Pedersen interpret as a skeptical silence. Pedersen said he wrote to experts at the National Institutes of Health, Harvard University and the McCardle Laboratory of Cancer Research at the University of Wisconsin to ask whether they had ever seen such results.

"Three of them didn't answer at all," he says. The major medical journals declined even to have the work peer-reviewed.

And that should be a cautionary sign, says Dr. Ute Moll, a cancer researcher and professor of pathology at the State University of New York at Stony Brook who's skeptical about the results.

"If it were really a major cancer breakthrough, it should have been published in the major journals," she says.

Moll says the team's paper failed to describe how the drug works, their study involved too few animals and omitted important details. And the drug still needs to be tried intravenously, on other cancers and other species.

"It's almost too preliminary," Moll cautions. "It has to go very far before it can even be called successful pre-clinical [animal] testing."

The prestigious journals might also have discounted the authors' credibility, Moll says, because they named their rats instead of numbering them — deemed unseemly in a serious scientific paper — and they used images showing how large the animals' huge tumors would appear on a human scale.

"It appears naive," she says.

Ko says she's working on a follow-up paper describing how 3-Bp works and is continuing experiments on other cancers.

She and her team face still more hurdles in finding a sponsor willing to finance human drug trials. One sticking point for potential pharmaceutical partners is that 3-Bp cannot be patented — it's already formulated and available inexpensively. Without a patent, drug makers can't be assured of the profits they'll need to pay for costly human drug trials.

"This is the state of affairs for many 'rain-forest' drugs — anything that is naturally occurring, or already synthesized and not patentable," says SUNY's Moll. "It's a very sad aspect, that we are under-utilizing and under-researching potentially hundreds of useful compounds."

At the Hutchinson Cancer Research Center, Hockenberry says, scientists working with such compounds often have to rely on interim funding from their own institutions, the NIH, advocacy groups focused on particular cancers, or foreign companies or governments with less-stringent rules for moving drugs to clinical trials.

Still, "If [3-Bp] proves to be wildly effective in the early phases of clinical trials ... some way would be found to get this going," Hockenberry says.

Faith in hard work

For Ko, it's a matter of bringing her discovery to the aid of desperately ill people. "Every day and every night I think about it," she writes in a midnight e-mail from her lab. "I have not lost completely my belief in Santa Claus, the Easter bunny, and the tooth fairy. I truly believe that if I continue to work hard that help will come."

Meanwhile, Ko says she has arranged a collaboration with Dr. Benjamin Carson, Dr. Margaret Panno and Pedersen to test 3-Bp on brain-stem tumors.

As for her rats, JM's cancer, which glowed so brightly in Pomper's PET scanner, was treated once with 3-Bp and stopped growing. Ko plans more treatments to try to shrink it. In the meantime, JM is "eating well and playfully running around her cage," she reports.

Another female rat with a breast tumor more than an inch wide has also received 3-Bp. "This tumor has been reduced in size by at least 85 percent," Ko says. "The remaining nodule ... is no longer growing."