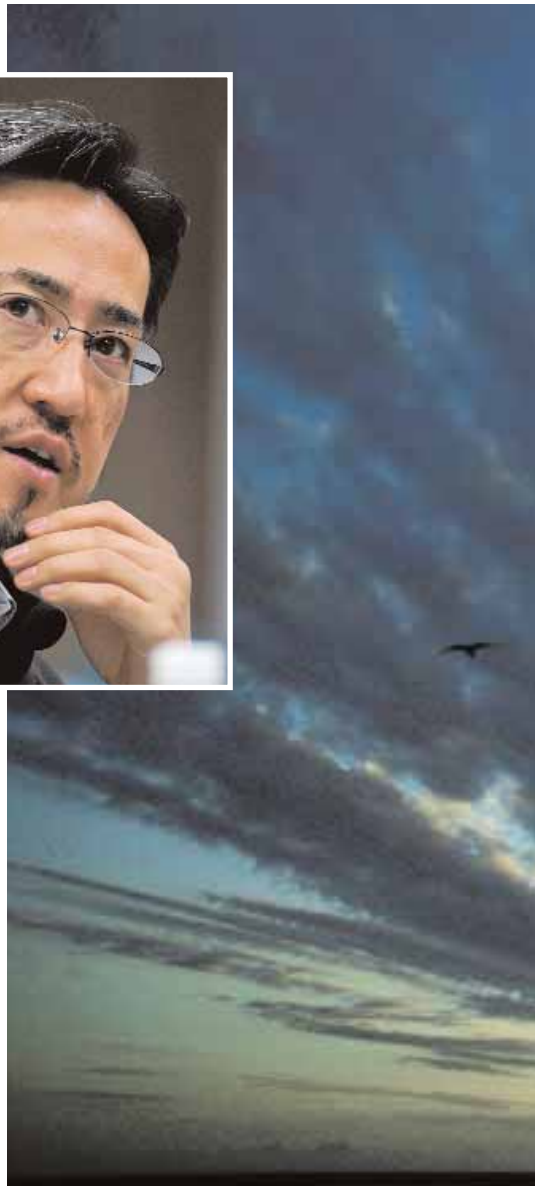
Flight Lessons



Professor Yoshihiro Kawaoka has logged thousands of miles chasing down the secrets of a deadly bird virus. But for the university, he is one who nearly got away. Why keeping Kawaoka is putting UW-Madison at the heart of the battle against pandemic flu.

By Michael Penn MA'97

Late in the autumn of 2004, as the elm leaves made their last stand and the early chill of winter fell across campus, Yoshihiro Kawaoka dropped by the office of Ronald Schultz, his department chair at the School of Veterinary Medicine, to deliver a letter. Schultz was expecting it, and expecting it to ruin his day.

Around the school, it was no secret that Kawaoka, one of the most prolific influenza researchers in the world, was being wooed. The University of Pittsburgh wanted the fifty-one-year-old professor to lead a new program on viral research, and officials there appeared willing to go great lengths to steal him away to the Steel City.

They had spent the summer courting him, jetting him and his senior lab staff to the Pitt campus and giving them royal treatment. Schultz, who helped lure Kawaoka to UW-Madison's pathobiological sciences department in 1997, knew that the letter contained the specifics of Pittsburgh's offer — and by extension, his first notion of what it would cost to keep his department's brightest star from leaving.

He unfolded the letter and began reading. What he saw took his breath away.

The letter laid out plans for the broad research institute that Pittsburgh was

DARRYL TORCKLER/THE IMAGE BANK/GETTY IMAGES INSET IMAGE: JEFF MILLER

proposing to put in Kawaoka's hands. He would have a floor of a new building, with lab space custom-designed for his needs. He would be able to bring his lab team from Madison, and he would have money to hire additional staff. He would have five faculty positions at his disposal to bring in collaborators. And as director, he would earn a six-figure salary that was practically unheard of for a veterinarian.

In short, Pittsburgh offered an empire.

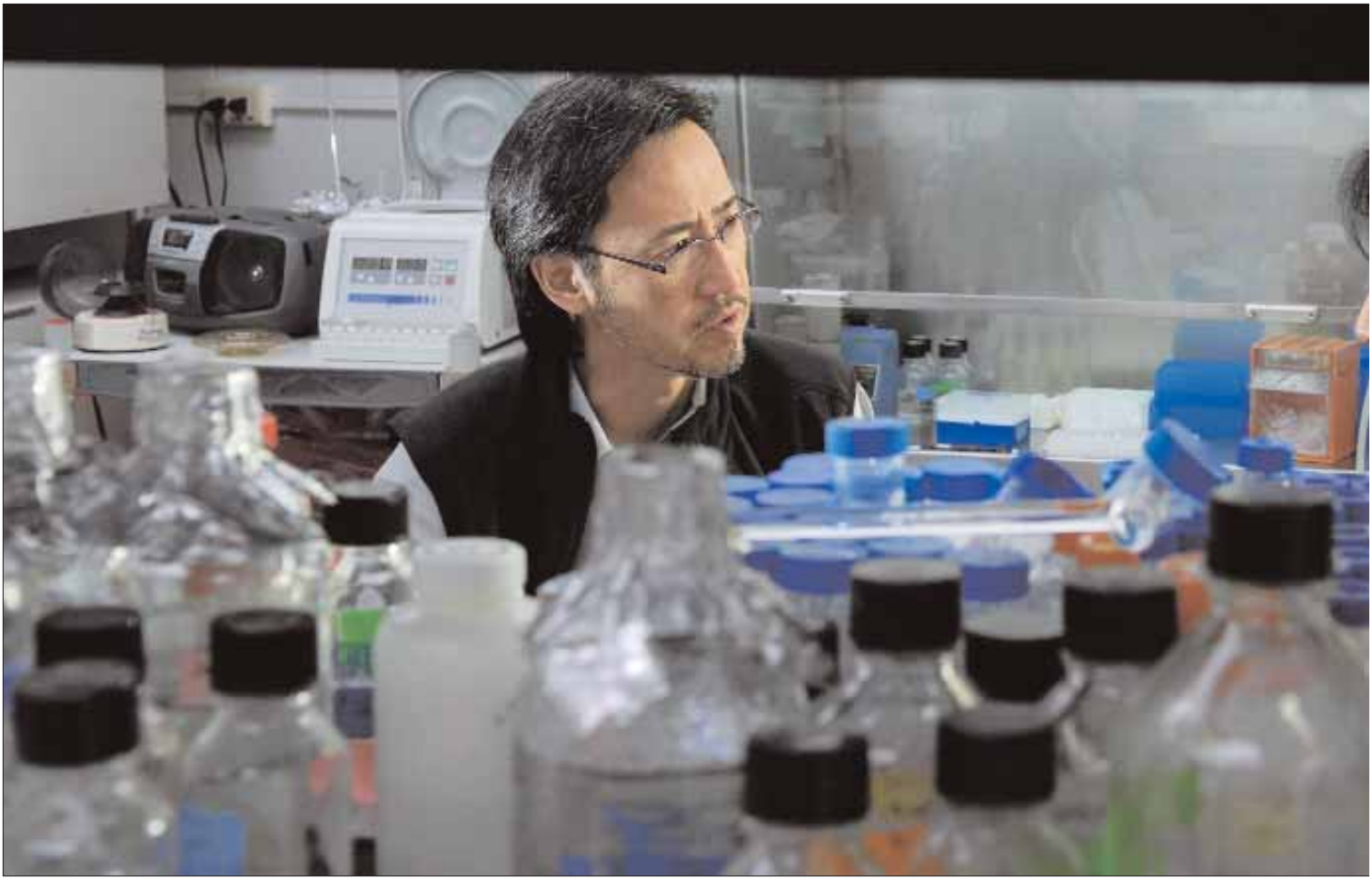
Schultz took out a yellow legal pad and began listing the things he would need to compete with the package. After three pages, he felt depressed. Like all department chairs, Schultz had a little money to spend to keep faculty from accepting outside offers — a couple of thousand dollars to deploy here and there. When you counted money to build new lab space, to land Kawaoka, Pittsburgh was promising to invest more than $20 million, eclipsing what the entire School of Veterinary Medicine spends on research in a year.

"I certainly didn't want to lose him under any circumstance, but I must say I didn't think we had much of a chance of keeping him when I looked at that letter and that package," says Schultz. "I thought, 'My god, wouldn't anybody want this?' "

Putting aside his doubts, Schultz typed a letter detailing what it would cost to keep Kawaoka, and, critically, what it would cost to lose him. On his way out of town to attend a conference, he hand-delivered it to the chancellor's office in Bascom Hall.

What came next was a tense game of administrative maneuvering that, while largely unseen, involved the highest levels of university administration, reached the desk of Wisconsin's governor, and enticed the university's patent agency to put $6 million of its own money on the

JEFF MILLER (3)



Kawaoka listens to an update from Shinji Watanabe (right), an assistant scientist in Kawaoka's lab who is investigating the genetics of the Ebola virus. Kawaoka's collaborators say his enthusiasm for new projects has something in common with the diseases they study: it's contagious.

table. It would consume Schultz and dozens of others for more than a year, this back-and-forth. And it all happened because of a virus, a looming health threat, and a quietly luminous scientist whom everyone knows as Yoshi.

Somewhere above the Pacific Ocean, he sits in the darkened cabin of a jumbo jetliner, intently awake. It is night, and all around him passengers nod off in the fitful slumber of long-distance travel. But Yoshi Kawaoka is not one to sleep on planes. Sleep takes time, and there is so little time as it is.

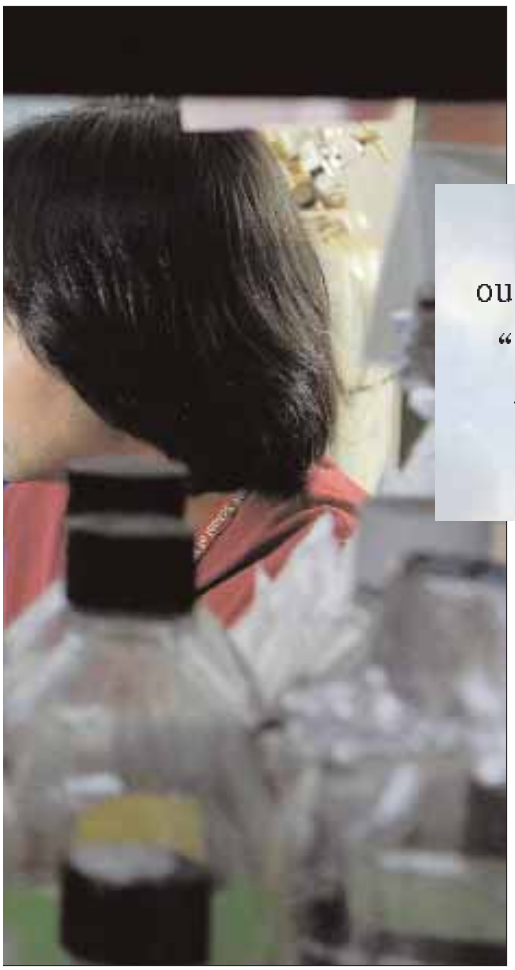
Trim and angular, with a goatee that wavers between full and artfully scruffy, Kawaoka is one of those rare people born with the capacity to be supernaturally alert. He rarely eats much, and he often sleeps only three or four hours a night, all while maintaining a lifestyle that most people would find ruthlessly taxing. He manages two laboratories — one at UW-Madison, the other in his native Japan, at the University of Tokyo's prestigious Institute of Medical Science — and travels between them at least once a month. Along the way, he fits in a murderous schedule of international conferences and collaborations. His usual itinerary reads like a once-in-a-lifetime journey: Stockholm, Geneva, Bangkok, Hong Kong, Hanoi — except he's often in these places for only one day, usually camped out in some conference site or government office.

"Honestly, I don't see how he is able to survive the kind of travel schedule he has and still get everything done," says Schultz. Kawaoka not only survives it; he seems to enjoy it. Clattering away at his laptop in the dim light gives him something rare in the life of a globe-circling professor: uninterrupted solitude, a chance to read, reflect, and tidy up the affairs of an unquiet mind. All the jetting about has its disadvantages — the feeling of constantly being between places, always on the way in or the way out — but really, it's just a long commute.

"I just try to be where I'm needed," he shrugs.

And if you're one of the planet's best authorities on the influenza virus, these days you're needed everywhere.

With the emergence of a particularly nasty strain of bird flu in Southeast Asia, influenza has moved up significantly on the list of things to fret about. Public health officials have grown anxious that



the virus that causes the lethal bird flu — a microscopic chain of genetic material that can get inside a body's cells and create all kinds of havoc — may someday soon begin spreading among humans. To do that, it would need to evolve genetically, but flu viruses are evolving all the time. Like all viruses, which have no cells of their own and must rely on some other creature's cellular machinery to reproduce, they have a chameleon-like ability to reinvent themselves, constantly stumbling onto new forms and abilities.

Often, these changes don't add up to much effect; while the seasonal flu bugs that circulate every winter look a little different each time around, for instance, the annual toll of influenza is pretty steady. According to the Centers for Disease Control and Prevention, about 114,000 people are hospitalized with flu each year in the United States, and about 36,000 people die as a result. But those figures pale in comparison to what can happen if a more dangerous mutant slips into the human population. Three times in the last century — in 1918, 1957, and 1968 — novel forms of flu triggered global pandemics. In the worst of those, the 1918 outbreak of Spanish flu, the virus spread around the globe in three months, and as many as 50 million people died, according to the CDC.

> Asked what he does for fun outside the lab, Kawaoka replies, "Nothing, nothing. There are too many interesting things to do here."

This is why scientists regard suspiciously every new form of flu that surfaces on the planet, whether it turns up in ducks, geese, pigs, or other mammals. And few have looked as intensively as Kawaoka, or learned as much by doing so. For the past two decades, he has deconstructed thousands of flu viruses — literally picking them apart gene by gene — in an effort to learn what makes them work and what we may be able to do to disarm them.

"If he's not at the top of the tree, he's damn near it," says Robert Webster, who heads the renowned influenza research program at St. Jude Children's Research Hospital in Memphis, Tennessee, where Kawaoka worked for fourteen years. Webster says that one of Kawaoka's breakthroughs — a technique called reverse genetics, which allows scientists to custom-build flu viruses in the lab — has revolutionized the field, opening the door for new drug development and faster production of flu vaccines. It's an invention that insiders whisper may someday put Kawaoka in the running for a Nobel Prize, which wouldn't at all surprise Webster.

Still, for all that progress, Kawaoka says "there is so much we don't know yet about these viruses." What, for instance, allows a virus that normally infects birds to start making humans sick? Why do some viruses make that leap, while others don't? And will the virus that surfaced in Hong Kong ten years ago — a highly pathogenic bug scientists call H5N1, which has infected more than two hundred people and killed more than half of them — be the one that sparks a pandemic? These are the questions that keep Kawaoka awake, the problems he ponders on those fourteen-hour flights.

Like the virus he studies, Kawaoka's path into influenza research evolved through birds. Raised in the cosmopolitan port city of Kobe, Japan, he enrolled at Hokkaido University to study veterinary medicine, continuing on to earn a PhD in microbiology. He was set to accept a faculty job in Japan when his adviser introduced him to Webster, the first scientist to pin the origin of human flus to their avian cousins. Although Kawaoka's studies had focused on bacteria, not viruses, Webster offered him a postdoctoral position in his Memphis lab, a golden opportunity to learn at the heel of one of the field's titans. And so in 1983, Kawaoka moved with his wife and two-year-old son to a new country and a new adventure.

Initially, Kawaoka planned to complete his two-year grant and return to Japan. But soon after he arrived, news broke of a potent flu virus spreading through poultry farms in rural Pennsylvania. Webster took the young researcher to New York City, where they made early-morning trips to live poultry markets to hunt for infected birds. When they examined the virus samples in the lab, they made a breakthrough discovery, pinpointing the exact molecular changes that had allowed a routine flu virus to turn into a lethal one.

With such discoveries, Kawaoka shone as the brightest in the constellation of Webster's young protégés. Virginia Hinshaw, a former colleague at both

St. Jude and UW-Madison and now provost of the University of California-Davis, recalls him as being "extremely bright and very creative. It was obvious that he was extraordinary." But in a field cluttered with brilliant minds, the difference between a good scientist and a spectacular one is often measured in something other than brains. Kawaoka had a different quality, a single-minded purpose that often had him in the lab before any of his colleagues arrived and well past their departures. It was almost as if he was determined to outwork the flu virus, to kill it into submission by the sheer force of his desire.

"When other people are satisfied with 90 percent or 100 percent, he goes for more," says Gabriele Neumann, a senior scientist at UW-Madison who has worked with Kawaoka since 1995. "He has the whole package. One has to be brilliant; one has to have ideas. But just having ideas isn't good enough."

In Memphis, Kawaoka still harbored doubts about his ability to succeed in the United States. He fretted about his English skills, worried that he didn't know the language well enough to keep up with the reading or make presentations. Webster had no such concern, and he convinced him to accept a full-time position, created when Hinshaw left the lab for UW-Madison. "I was absolutely convinced he was on his way," Webster says. "He was special."

It was Hinshaw who again set the stage for Kawaoka's next move. In 1995, she left her flu lab in the School of Veterinary Medicine to become dean of the Graduate School. With her encouragement, Kawaoka applied for her job, eventually joining the faculty in 1997. "I remember him coming to my office in the Graduate School and looking around, saying, 'I just want to see where I'm going next,' " Hinshaw laughs.

Where he was headed next, however, was Hong Kong. Four months after he arrived in Madison, Kawaoka was chosen by the National Institutes of Health to join a select team of international researchers analyzing the H5N1 virus, which had been identified in poultry in China and had begun to appear in humans. By the end of the year, the bird flu had infected eighteen people, killing six — a foreboding sign of the virus's potential that raised the alarm of public health officials around the world.

Back in Madison, Kawaoka received seventeen samples of the virus and set to work deconstructing them. He and his lab staff discovered that by replacing two genes on a common, low-level flu virus with particles from H5N1, they could create a hybrid strain of the flu that killed mice within thirty-six hours of infection. That's all it took — two simple mutations to turn a mild case of the flu into a deadly one. Given the shifty genetics of viruses, this meant that even ordinary flu viruses were never far from turning fatal, a sober reminder of the slim distance between routine and chaos.

Not all Kawaoka's findings have such glum implications. Earlier this year, he published a paper that largely explains why H5N1 hasn't yet caused a pandemic — and may never. His team found that the virus lacks the genetics to bind efficiently to cells in the upper respiratory system, meaning that while it can make humans very sick once it gets into cells, it has a hard time gaining entry.

But don't write the virus off yet: despite the slaughter of millions of birds in an attempt to eradicate it, the virus resurfaced in 2003 and has since spread through Asia and into Europe and Africa. It has sickened people in eighteen countries, from Indonesia to Turkey, killing more than half of those infected. And while there is still no confirmed instance of human-to-human transmission, any of the millions of viruses wafting around in the avian population might mutate just enough to be a nightmare.

"We don't want to make people think there is nothing we can do. And we don't want to give false warnings all the time," says Kawaoka. "But for people in the field ... it's a very scary situation right now." He says when he gives talks about the threat of pandemic flu, he hears no applause at the end. Just dead silence.

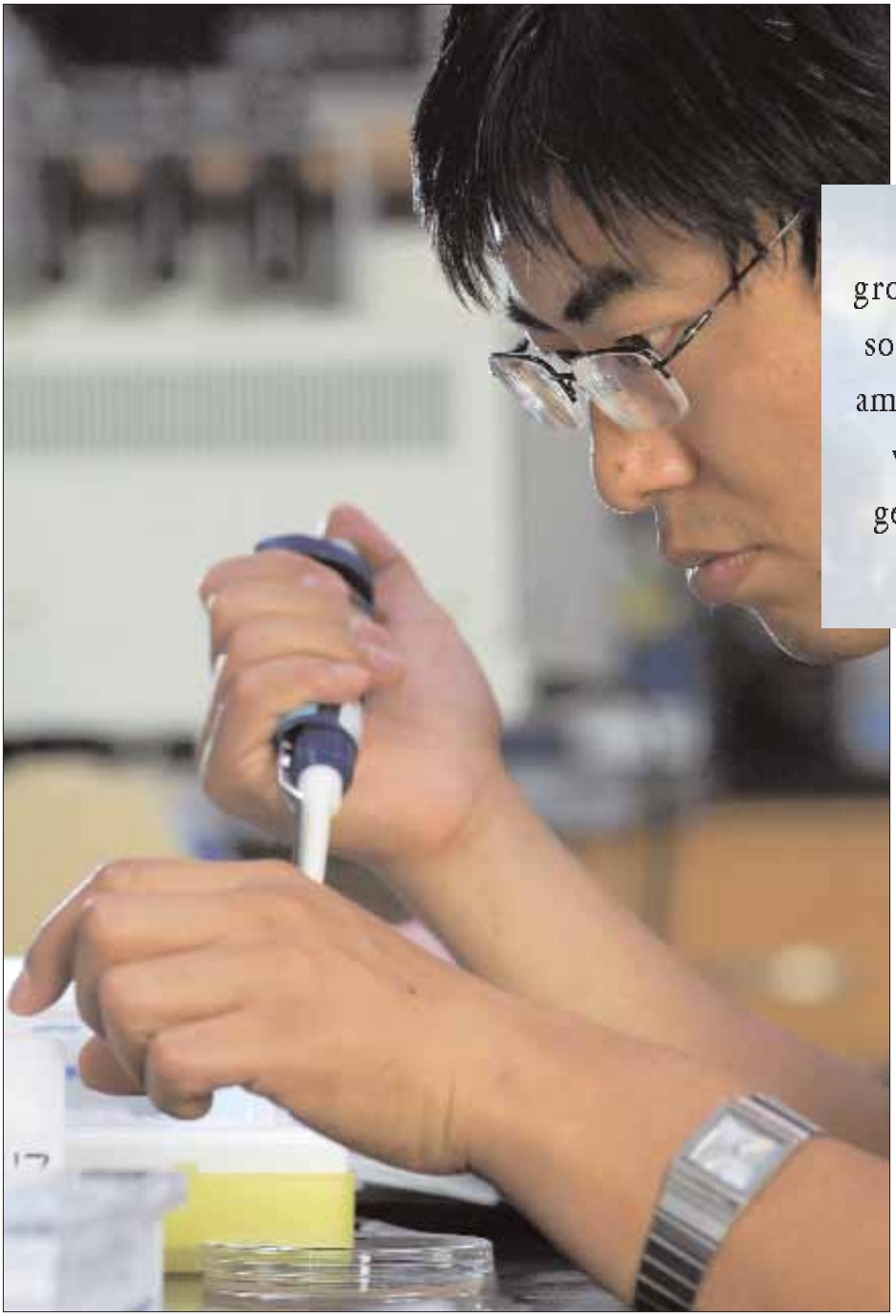
"That's the reality," he says. But then, sensing the air of morbidity settling over the conversation, he moves to diffuse it. "I keep telling my wife to stockpile food and water. But she only has one can of tuna."

Laughter comes easily for Kawaoka, especially when the subject is his science. Despite its fearsome potential, the influenza virus fascinates him, and when he talks about it, his voice takes on an excitement that reveals the inherent coolness he finds in his work. Asked what he does for fun outside the lab, Kawaoka replies, "Nothing, nothing. There are too many interesting things to do here."

When she was dean of the Graduate School, Virginia Hinshaw from time to time invited Kawaoka on faculty retreats intended to refresh the soul. He always politely declined, which worried Hinshaw at first. Then, she says, "I came to realize that his scientific endeavors and adventures were truly providing that refreshment for him." The lab is where his soul finds nourishment.

"It's exciting to watch him think," says James Tracy, associate dean of the School of Veterinary Medicine. "He's always working on the next experiment. As soon as someone publishes a paper that's got some new little twist, it's got him going off in yet another direction."

Science can barely keep pace. In 2005, Kawaoka's research labs in Madison and Tokyo published twenty-seven research findings, astounding productivity in the creeping realm of academia. And the boundaries of his curiosity keep growing. After reading Richard Preston's book *The Hot Zone,* the best-selling account of an Ebola scare and the only mass-market English-language book Kawaoka has finished reading, he launched a study into the Ebola virus. He says the book's description of animals infected with Ebola struck him as similar to what happens when they suffer from highly pathogenic flu strains. "When I read that, I thought, 'Maybe I can do something,' " he says.



Zejun Li, a postdoctoral fellow in Kawaoka's lab, cultures colonies of *E. coli* bacteria containing genes from influenza viruses, a technique used to identify what specific flu genes do.

It was that thirst to do more that led Kawaoka to pay attention when the University of Pittsburgh approached him in 2004. The university's medical school was in the process of building a $200 million biomedical research lab and wanted Kawaoka to lead a program designing and evaluating vaccines for infectious agents such as flu, SARS, Ebola, and HIV. Initially, Kawaoka said he wasn't interested in leaving UW-Madison, but Pittsburgh officials were persistent, convincing him to hear them out. The more he listened, the more he grew intrigued by the endeavor's ambitious reach.

"I think he was very serious about it," says Neumann, his UW-Madison colleague. "Every researcher wants the best for his group and for his research, and so if there is a good offer, you should always look into it."

> Public health officials have grown anxious that bird flu may someday soon begin spreading among humans. To do that, the virus would need to evolve genetically, but flu viruses are evolving all the time.

These days, more and more faculty are listening. In the 2004–05 academic year, 106 UW-Madison professors received offers from other employers — about one of every twenty faculty on campus, according to a study by the provost's office. The number has doubled during the past four years, and the university's success in retaining those professors has waned. Historically, about three of every four faculty wooed by another university opted to stay at the UW. Now only about half do. The growing perception among deans is that UW-Madison's flat budget has made it a target for better-heeled universities that want to cherry-pick its best scholars.

But if faculty retention is an institutional headache, the prospect of seeing Kawaoka leave for greener pastures bordered on something of an identity crisis. To lose such a prominent figure would have significantly dented the university's image as a research powerhouse. "If there is anyone within the biomedical sciences we needed to retain — especially with the topic being so timely — this was the person," says department chair Ronald Schultz. "There are not many people like this."

Even in the fall of 2004, Schultz saw hopeful signs that he could entice

Kawaoka to stay. At one point, after Pitt had flown Kawaoka's lab team in for a visit, one of the staff confided in Schultz that some in the group weren't thrilled by the visit, a tiny wedge that Schultz wasn't above exploiting. Surfing the Internet, he found a magazine survey that listed Pittsburgh as one of the country's most emotionally depressed cities and gave it to Kawaoka.

The bigger problem, though, was money. With the pile of federal and private grant money Pittsburgh had behind its offer, matching it was out of the question, simply unaffordable. "We were trying to figure out, what's his bottom line? What's the minimum he would accept?" says Schultz.

It was clear that Kawaoka needed new lab space; his eighteen-person staff was bursting through the doors of three shared labs in the veterinary medicine building. "His ability to get grants outpaced our ability to provide space for him," says James Tracy. But adding space, particularly the specialized biocontainment facilities necessary to work on hazardous materials such as influenza viruses, was expensive. No one pretended that a small school such as Veterinary Medicine — or even the university as a whole — could pull it off alone.

And neither would they have to. In January 2005, Chancellor John Wiley MS'65, PhD'68 was attending the governor's State of the State address when he felt a tap on his shoulder. He turned to see Carl Gulbrandsen PhD'78, JD'81, managing director of the Wisconsin Alumni Research Foundation, who whispered, "Have you heard we might lose Yoshi?" WARF, which annually returns some $50 million in patent royalties to the university, had its own reasons to be concerned. The agency had filed patents on Kawaoka's inventions and saw potential to license his technology to companies producing flu vaccines. And while WARF isn't in the business of doling out faculty raises, it had stepped in to help in a few select cases in the past.

"[Some universities] can snap their fingers and come up with money. It's very difficult for a public university like Wisconsin to compete against it," says Gulbrandsen. "I think without a WARF, it would have been almost impossible for the university to respond."

Following that chance encounter, an extraordinary cooperation began to take shape. Gulbrandsen went to WARF's trustees and asked for $6 million to help build Kawaoka a laboratory. The university came up with another $3 million and pledged to fund three new faculty lines in Kawaoka's field, forming a core group of collaborators that would allow him to expand the scope of his research. University Research Park offered a vacant building that could be remodeled to house Kawaoka's team, which would get a new official designation as the Institute for Influenza Viral Research. Wiley and Governor Jim Doyle '67 both called Kawaoka to sell the virtues of continued Badgerhood.

Next, university officials sat Kawaoka down with an architect and asked him to spell out exactly what he required to do his best work. It proved to be a nearly disastrous misstep. After consulting with Kawaoka, the architect returned with plans for a sprawling, fifty-thousand-square-foot facility that would cost upward of $38 million — about $27 million more than the university had marshaled for the project. With Pittsburgh's offer still on the table, Kawaoka and Wisconsin suddenly were at an impasse.

The university had no choice but to tell Kawaoka it couldn't afford his dream lab. "That was not a fun conversation," recalls James Tracy. Kawaoka felt the university was backing away from its promises to meet his needs. At first, he told officials they needed to find more money.

Tracy doesn't read the reaction as egoistic. "I've known Yoshi since the day he got here, and he is not an arrogant person," he says.

"He just wanted to be sure that we put everything we possibly could into making that program a success," says Schultz. "He will push, but he also recognizes when to stop. And I think he knew we were doing everything we could."

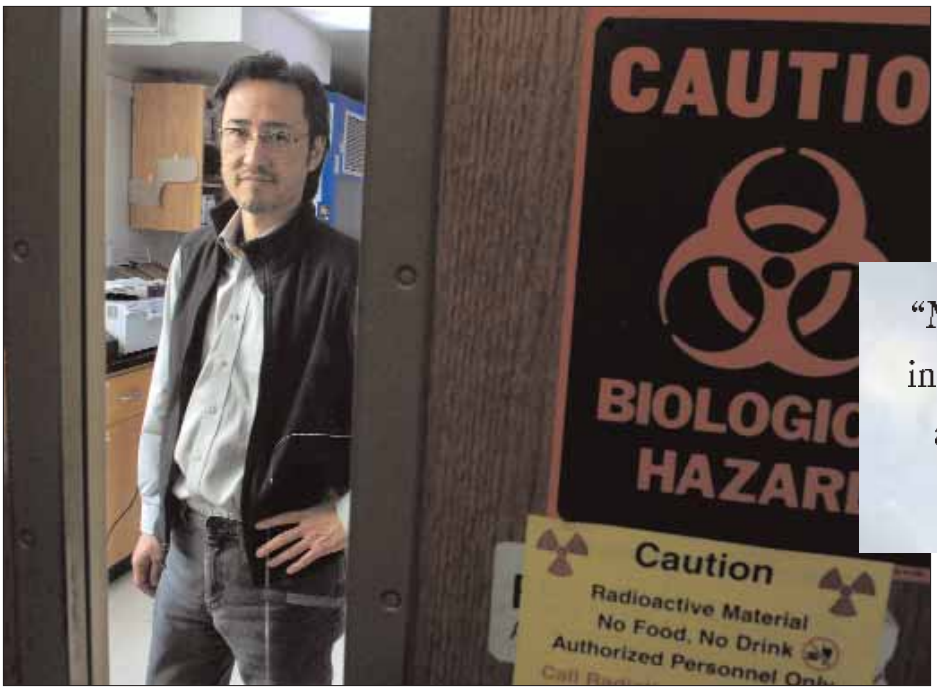
In the end, after a year of negotiation and the combined efforts of more than fifty people, Kawaoka agreed to a package that, while one of the most expensive faculty retention deals in university history, fell well short of what he had been offered at Pittsburgh. He says he chose to stay because he likes Madison, and he likes the institutional support he's been given over the years.

As an example, he cites the legwork invested in planning his new laboratory. The $11.4 million project, which has taken fifteen months to design, will expand and completely reconfigure a building at University Research Park. Construction began this fall, and if all goes well — and much still needs to go well — Kawaoka and his team will move in by next summer.

What most excites Kawaoka — and what most complicates the job's completion — is that the building will include a so-called BSL3-Ag lab, a highly secure space designed to allow researchers to work safely on life-threatening biological agents. BSL3-Ag, which stands for Biosafety Level 3-Agriculture, denotes the second-highest level on the federal government's biosafety regulations and is prescribed for work with viruses that would pose health threats if they escaped the lab. Since no facility of this standard currently exists on campus, Kawaoka has had to ship some research projects — including one to build and evaluate a replica of the 1918 Spanish flu virus — to a lab in Canada.

"Many universities don't want investigators to work on select agents, because it's a heavy administrative burden," says Kawaoka. "But this university, the support is just great. It's a tremendous amount of work."

Embedded in the basement of the three-story building, the lab will resemble a land-bound submarine crafted of concrete. The only way in or out will be through camera-monitored airlock



Kawaoka's ability to get projects funded has outpaced the university's ability to provide enough secure lab space to perform those experiments, making expansion a priority.

doorways, and lab workers will be required to wear safety gear and shower before leaving the area. Every bit of air circulating inside will be filtered and purified. Every drop of water used will be boiled and cooled before entering the sewer system. Every last scrap of material taken out of the lab, from used pipettes to rodent droppings, must be specially treated before disposal. And every contingency must be accounted for: What if the power fails? What if a tornado strikes the building? The university's answers must pass muster with two government agencies — and everyone who intends to work there must pass a Federal Bureau of Investigation background check — before anyone can so much as stain a Petri dish. (Still, government standards can't stand up to the critical eye of the beholder. When architects gave Kawaoka their final plans, he and his staff probed every detail and came back with forty-two changes, right down to the location of the coat hooks.)

The requirements represent "the most stringent set of federal guidelines I've ever seen," says Tracy, who coordinates UW-Madison's biosafety efforts. "It's even more stringent than working with radioactivity. The level of security is as high as it gets for a campus laboratory." Because of the filtration and entry security measures, only half the building's footprint is usable space. While typical campus labs cost about three hundred dollars a square foot to build, this one will end up running four times as much. "This is the most expensive lab space in the world," Tracy says.

Yet along with concrete and steel, Kawaoka's laboratory will be forged from expectation. When the new institute was announced in March of this year, Governor Doyle proudly took the podium and proclaimed that Wisconsin "has the best minds working to understand this virus." The clear implication was that those experts would produce results.

"If pandemic flu had not been as big an issue, I'm not sure the university would have gone quite as far," says Tracy. "If it hadn't been Yoshi and just an average researcher, they wouldn't have gone this far." He cites James Conant, the former president of Harvard University, who once said: "To advance scientific knowledge, pick a man of genius, give him money, and let him alone."

"That's what you have to believe with someone like Yoshi," he says. "If you give him money, he'll do something great with it."

If Kawaoka feels pressure, he isn't letting on. He says his lab's role is to provide tools and knowledge, not necessarily to prevent a pandemic. And while he'd love to make some life-saving discovery, "even without that," he says, "I would be motivated. I just happen to be working on this, and it just happens to be pandemic-related. I didn't choose that."

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He says the way he approaches his work isn't all that different from how his father ran an exporting business back in Kobe: "What I'm doing is exactly the same thing my father was doing, and that is get money, find good people, get good ideas, and do the work. There's nothing different between business and science."

Except it's not that simple. His legendary drive has not mellowed. If anything, it's kicked up a gear. He hasn't taken a vacation in years, and one gets the impression that the threat of pandemic flu crowds his conscience, pushing other aspects of his life to the margins.

"My only concern about him is that he works too hard," says his mentor Robert Webster. He says that years ago, as a young scientist in Memphis, Kawaoka grew bonsai trees, tiny Japanese shrubs that require meticulous pruning. Some time after he moved to Madison, the hobby fell victim to the ever-increasing demands on his life. "I just wish he would start growing those trees again. He needs to relax," says Webster. And Kawaoka might very well try, if there weren't so much else to do.

Senior Editor Michael Penn MA'97 vows to remember to get a flu shot this year.