Under a dynamic "CEO," Sweden's biomedical powerhouse is forging alliances intended to make it competitive with the Harvards and Cambridges of the world

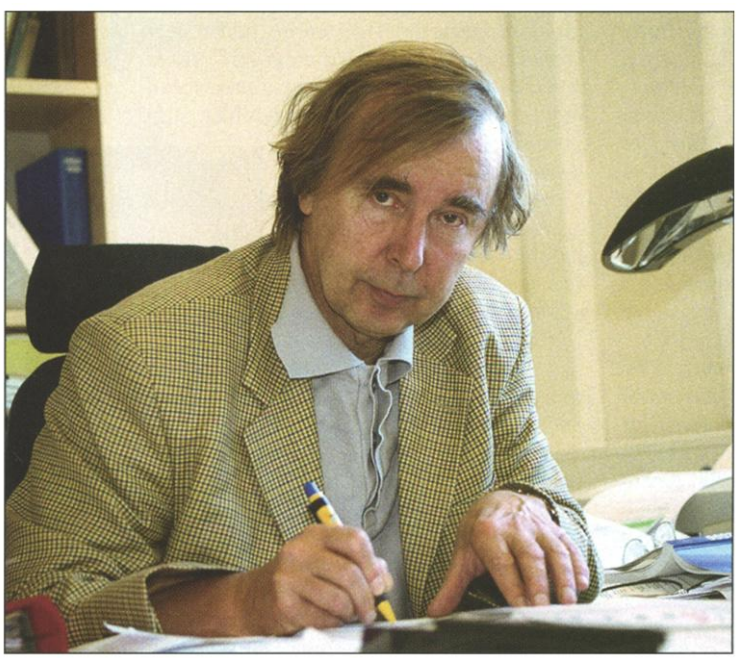
Karolinska Inc.

STOCKHOLM—Hans Wigzell has a way of winning over the harshest critics. At a reception in the Stockholm City Theater in 1989, actors accused Wigzell and his colleagues at the Karolinska Institute (KI) of seeking to create "Frankenstein monsters," he recalls. "I told them, 'You don't know anything about science.' " After several hours of back and forth, the actors' attitudes were completely reversed. The immunologist and his newfound friends even went on to create a play, with a biology theme, in which Wigzell plays himself. (A modest hit, the production has drawn 25,000 people over the past decade.) "Some colleagues said, 'You can't do this, a Karolinska professor can't act like a clown,' " Wigzell says. "That made me completely convinced that we had to do it."

Such a headstrong nature, tempered by charm and candor, is serving Wigzell well in a more ambitious mission: shaking up the Karolinska, Sweden's top biomedical center. Since being elected institute president in 1995, Wigzell has moved aggressively to forge ties with industry, creating a series of holding companies that allow Karolinska to invest in biotech start-ups and to market its scientific talent. Insiders say Wigzell arrived at just the right moment. In the early 1990s, the Swedish government began slashing basic research spending. Karolinska had to change fast or lose its landmark status in the world's biomedical research landscape. "The ivory tower attitude is just not working anymore," says KI's Claes Wahlestedt.

"We have had to go as fast as possible to control our own destiny," Wigzell explains. In addition to cutting scores of deals with companies and steering money into start-up firms, he has forced Karolinska researchers to compete for internal funding instead of spreading it evenly across departments. "It has been a revolution, but the changes were inevitable," says immunologist Maria Masucci of KI's Center for Microbiology and Tumor Biology. Outsiders are impressed. "He's been transforming the Karolinska, taking it in a dynamic new direction," says J. Craig Venter, president of Celera Genomics of Rockville, Maryland.

Not everyone, however, is enamored with the Wigzell revolution and its emphasis on industry ties. "There's been a discussion out there about whether this is a form of prostitution," admits KI university director Rune Fransson, a member of Wigzell's inner circle who has helped make his vision a reality. Many, however, laud Wigzell's tenure and look forward to what could be the crowning achievement of his presidency: Stockholm BioScience, Europe's largest science park, a multibillion-dollar venture that got a preliminary go-ahead last month.



Controlling destiny. Hans Wigzell knew that with less government money, Karolinska had to team up with industry to maintain its landmark status.

CREDIT: LARS SKOG

Still, Karolinska has a way to go to catch up with the likes of Harvard, says Hans-Olov Adami, chair of Karolinska's Center for Medical Epidemiology and an adjunct professor at Harvard. "KI is lagging behind," he says, "but we know it and have a clear ambition to improve."

A Nobel and nobler tradition

Karolinska was created after Sweden's defeat at the hands of Russia in the Finnish war, which ended in 1809. During the war, roughly one-third of wounded Swedish soldiers died in field hospitals, a record that prompted King Charles XIII to found the Karolinska Institute in 1810 to provide better training for army doctors.

From early on, the Karolinska put great emphasis on basic research, but what really put it on the map was a clause in Alfred Nobel's will that gave Karolinska the task of picking the Nobel laureates in physiology or medicine. "Every important scientist comes through [on research stints] because of the Nobel aura," says Wahlestedt.

Sweden's successive social democratic governments also treated Karolinska generously. "Medical research has been strongly supported for decades," says Kjell Simonsson of the Karolinska Investment Fund. In the early 1990s, however, a sluggish economy prompted the Swedish government to cut research budgets. Wigzell's predecessor, Nobelist Bengt Samuelsson, saw the writing on the wall and began setting up a legal framework that would allow Karolinska to forge industry ties.

In 1995, as senior Karolinska faculty members were casting around for someone to step up the pace of Samuelsson's reforms at this critical stage, Wigzell's name kept coming up. He had established his scientific credentials in tumor biology and immunology 2 decades earlier with his co-discovery of natural killer cells and development of a widely used chromium assay for measuring cell death. (With 500 peer-reviewed publications and counting, he still maintains a lab.) Wigzell also proved an adept administrator as director of the National Bacteriological Laboratory in Stockholm, the Swedish version of the U.S. Centers for Disease Control and Prevention. When Wigzell took over in 1988, the lab was in decline; he dissolved it and rebuilt

Working Sweden's Population Gold Mine

One of Hans Wigzell's boldest scientific moves as head of the Karolinska Institute was to encourage a bright Swedish star in cancer epidemiology to uproot his entire department at Uppsala University and move to Stockholm. Since making the switch in 1997, Hans-Olov Adami's team has grown from 40 to 150, consolidating its position among the top epidemiology departments in the world.

Adami had built a reputation at Uppsala on high-impact papers on everything from the cancer risks of hormone replacement therapy to survival rates for early prostate cancer. However, he says, Uppsala's financial support was flagging while Karolinska beckoned with a "much more vital, visionary, and dynamic" environment. "Our faculty locked ourselves up like cardinals and voted to move," Adami says.

Key to Adami's success is his group's access to Sweden's unique national databases, a gold mine of information for exploring how genes and the environment influence disease. The country's national health care system gives each person an identification number at birth and maintains health records in a registry. This allows for so-called "linkage" studies in which cancer cases can be assessed by occupation, for instance, or time of first pregnancy. Karolinska also maintains two high-powered research databases, including the world's largest twin registry with records on over 70,000 pairs.

Once ensconced at Karolinska, Adami did some recruiting of his own, luring behavioral geneticist Nancy Pedersen from another Karolinska department in 1999. She helped the group expand beyond cancer studies. All told, the team churns out a paper every couple of days, over 100 in 2000 alone. Among their recent contributions are studies probing the links between human papillomavirus and cervical cancer, and, for example, caffeine consumption and spontaneous abortions.

The twins database, with the oldest living pairs in their 90s, is becoming ever more valuable now that "enough people are dying or being sick" from chronic diseases, Pedersen says. Some findings based on the twins have been controversial: For example, scientists recently challenged a paper suggesting that cancer risk is linked only weakly to genes (*Science*, 27 July, p. 601). "It was a good contribution, but it indicates how difficult these studies are," says epidemiologist Robert Hoover of the U.S. National Cancer Institute. Another influential study suggested that intelligence is determined largely by genetics, even into old age (*Science*, 6 June 1997, p. 1560). The Karolinska team's skill at working these databases has produced "penetrating findings," says Harvard epidemiologist Walter Willett, who expects to see a steady stream of intriguing papers from Stockholm in the years to come.

Doubly precious. Studies of identical twins Ruth and Annié Nyström and others in Karolinska's registry are yielding insights on genes, aging, and disease.

CREDIT: GUNN ABERG

–JOCELYN KAISER

With reporting by Lone Frank, a science writer in Copenhagen.

it from scratch.

Despite professing a desire to return to the lab bench, Wigzell was nominated and elected and took over Sweden's biomedical powerhouse in July 1995. His first task was to work the same magic that he had performed on the actors at the Stockholm theater. He set out to change the attitude "that KI is as good as it could get and shouldn't collaborate with anyone, ... certainly not industry," says Per Hall, vice chair of the Center for Medical Epidemiology at Karolinska.

Industrial deals

Although the institute director does not have the power to direct research, Wigzell took steps to stamp out mediocre work. In 1993, Samuelsson had melded 158 departments into about 30. Under Wigzell, the reforms have proved to be more than just a revised seating plan. Department chairs now control most of KI's federal funding, which provides enough money for a few months' salary. Professors must then compete for funds for the remainder of their paychecks. "It's not that easy to sack people," says Fransson, who says the goal is to "be more elitist, allocating more money to fewer researchers."

Making KI's faculty leaner and fitter is all part of Wigzell's mission to put the institute on a sounder financial footing. With levels of government funding now harder to predict, Wigzell had to find other sources of income. He soon realized that KI's greatest growth potential lies in corporate ties. Five years ago, only about 2% of the institute's funds came from industry; that percentage has grown to 7% in this year's $285 million budget. He is aiming for a 20% share by 2004.

As a first step, KI had to do a better job of licensing its inventions. As in Finland and Norway, Swedish researchers own their own research. But Wigzell realized that having researchers hawk their wares directly to drug companies wasn't working. "Big pharma doesn't want academic people coming to them; they don't know where they've been," says KI's Folke Meijer. Instead, he says, "pharma wants to buy ideas after the proof-of-principle stage." To make Karolinska's ideas more attractive, one of Wigzell's first initiatives as president was to pressure the government to pass legislation allowing universities to set up commercial entities. Within days of the law being passed, he had established KI Holdings AB, a commercial arm of the nonprofit institute. Since then, Wigzell and his top lieutenants have created several companies nested like Matryoshka dolls under KI Holdings.

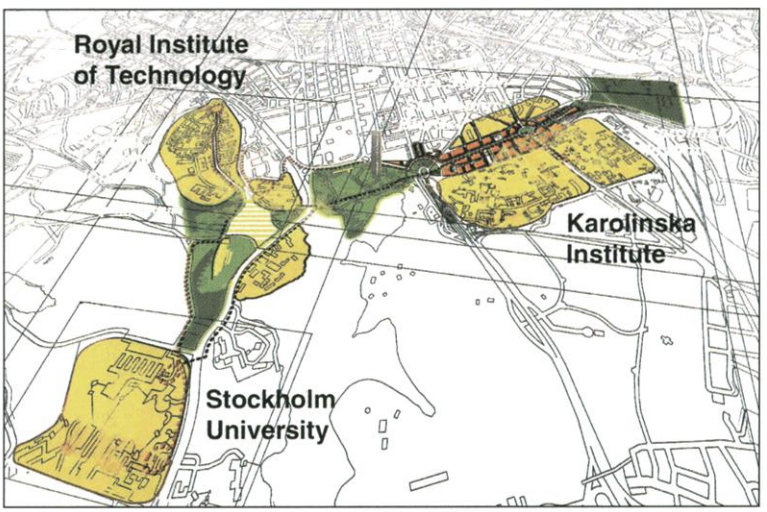
For example, Karolinska Innovations AB (KIAB) essentially serves as the university's tech-transfer office, filing for patents on behalf of inventors, then selling or licensing them, with a portion of the money flowing back to the inventors. As well as selling their ideas, KI is now encouraging researchers to go into business themselves. In 1999, Wigzell and company set up the Karolinska Fund, with five investors—a major Swedish pension fund, the Wallenberg Foundation, two insurance companies, and the Swedish Medical Association—pooling $50 million in venture capital. Three new buildings, to house a staff of up to 600, are rising to accommodate KI start-ups and should be finished by the end of 2004. Wigzell hopes that within a decade, as many people will be employed by KI companies as are employed by KI itself.

One budding success story is a firm called Global Genomics. Molecular biologist Sten Linnarsson, working as a Ph.D. student in Patrick Ernfors's lab at Karolinska a couple of years ago, was disappointed with the results from experiments using Affymetrix gene chips. "This started my brain working on how to do this better," Linnarsson says. He hit upon a method of combining gene detection using the polymerase chain reaction with computer algorithms designed to identify and quantify the genes in a sample. The young team—Linnarsson is 30 and Ernfors is 37—took the idea to KIAB. After agreeing to terms, KIAB filed for patent protection and helped the duo set up Global Genomics. Within a month after its formation, the company had secured venture capital.

While nurturing start-ups, Wigzell has also sought closer ties with big pharma, such as by collaborating on the Center for Genome Research and Bioinformatics (CGB), a joint operation with Pharmacia & Upjohn Inc. Set up in 1997, the center was at first funded solely by the drug giant. "In the beginning, there was a lot of suspicion and natural skepticism from researchers around KI" who doubted that the center could retain its academic freedom, says Wahlestedt, CGB's director. But perceptions have changed, he says: "As we went along and they saw [that] we hire talented basic scientists and produce good science, ... people were won over."

The industry ties have not just been restricted to Sweden or the pharmaceuticals business. Last year, Wigzell struck a deal with the Japanese firm Sumitomo, which sank $7 million into clinical research at KI related to Alzheimer's disease. The collaboration has opened a floodgate of other Japanese organizations looking for ties with Karolinska.

Now, KI is embarking on an even grander industrial venture. The plan is to convert a huge unused railway yard, covering more than 500,000 square meters, into a business park dominated by biotech start-ups and research institutes, along with housing for scientists and students. Last month the city of Stockholm and Jernhusen AB, which owns the land, signed a letter of intent to develop BioScience. This "was the first and absolutely necessary decision" to proceed from the visionary stage to implementation, says John Skår, director of Karolinska's Center for Medical Innovations, who dreamed up BioScience. Along with Stockholm University and the Royal Institute of Technology, KI is now looking for roughly $2 billion in private investment and hopes to open the park for business by 2006. The three academic players expect BioScience to stimulate collaboration between themselves and industry, potentially creating thousands of jobs for scientists.



Room for growth. Karolinska and its partners are seeking $2 billion to launch the mammoth Stockholm BioScience park (depicted in red).

CREDIT: KAROLINSKA INSTITUTE

Conflict resolution

With this amount of traffic between academia and industry, potential conflicts of interest could become a serious issue. Wigzell is overseeing an effort to craft rules requiring full disclosure. Draft guidelines mandate a KI review if a scientist receives more than half his or her research support from industry. Already in place is a rule that the administration must sign off on any deal exceeding $10,000.

When not leading KI, Wigzell serves on many corporate advisory boards around the world. And in March 1999 he was appointed science adviser to the Swedish government. Besides pressing for legislation that would benefit scientists, he tries to educate politicians by introducing them to scientific leaders. Recently, he took Harold Varmus to lunch with Prime Minister Göran Persson and dined out with Venter and Research Minister Thomas Östros. "Politicians need information they can trust," Wigzell explains.

Not all Karolinska staff members have enjoyed being caught up in the Wigzell whirlwind. "The leadership of Wigzell is about taking people by surprise, and not everyone likes that. He is a person you either love or hate," says Masucci, adding that "it's a minority who are discontent."

But that minority spoke resoundingly when Wigzell's first term expired last June. Although he won reelection for a 2.5-year term that will see him into retirement, several prominent voices in KI's electoral assembly voted for a clinician to take the helm. The vote reflected disaffection within the clinical research ranks, which comprises about 60% of KI's scientific staff. Part of the frustration stems from increasing clinical and teaching demands. "There's no time for a clinician to keep up with the knowledge," says Fransson, who notes that this problem is not unique to Karolinska. "If you were to find a shadow over Hans, this would be it." In response, Wigzell is stepping up efforts to help KI clinical researchers benefit from the industrial ties. He's also designed a "merit portfolio" that attempts to account for teaching, scientific, and clinical achievements in marking career progress.

Wigzell has also come under fire because few women have risen to Karolinska's higher echelons. "The new business-type organization tends to favor an old boys' network," asserts Masucci. "This breeds discontent." That view is shared by some prominent outsiders. "It was a nationwide scandal when he appointed 15 [department chairs] last February and they were all male. He did not do this by mistake," charges KI board member Agnes Wold, a bacteriologist at Göteborg University.

Others defend Wigzell's record. Tomas Cronholm, KI's trade union leader, notes that the university has just appointed equality ombudspersons to help female staff members and students. "He now takes this issue very seriously," Cronholm says. Wigzell himself insists that he is working hard to raise the status of women at Karolinska. He even cites Kerstin Wigzell, Sweden's surgeon general (and his wife), as his role model. "She's taught me how to open up to people," he says.

That has undoubtedly helped Wigzell become a master at the art of bending people's wills to the task of raising Karolinska's fortunes. Says Brazilian Dulceaydee Gigliotti, who works in Wigzell's lab, "Only an unconventional Swede like Hans could bring about changes so fast. He broke the dogma."

–RICHARD STONE AND LONE FRANK

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