gression. Tapping the Danish Cancer Register and a central blood bank database, Melbye's team recently debunked the idea that getting a blood transfusion increases cancer risk. And in another large project, they resolved the long-standing question of why young women with breast cancer have a poorer prognosis than older women with the disease. Compiling data on 35,000 breast cancer cases, the researchers found that young victims live longer if chemotherapy is started as soon as the cancer is diagnosed, rather than reserving this treatment approach only for tumors that have grown to a certain size.

The health databases are also useful for unraveling complex diseases. Psychiatric epidemiologist Preben Bo Mortensen of Aarhus University Hospital has mined the Danish Central Psychiatric Register, which contains information on all Danes who have come into contact with the public psychiatric hospital system since the 1930s. He has identified a host of environmental factors, such as prenatal viral infections and season of birth, which appear to influence the development of schizophrenia and bipolar disorder. "The register allows us to tease out the relative contribution of genetic and nongenetic factors and thereby point to possible strategies for preventing disease," says Mortensen.

But at a meeting on database research in Copenhagen earlier this year, scientists complained that they have been prevented from taking full advantage of the wealth of registered information. Part of the problem is that the agencies that maintain databases are reeling from budget cuts. "Increased funds are needed to secure the quality of existing and future databases if we want to keep our lead in the field," says Olaf Ingerslev of the Board of Health. Experts estimate it would take only a modest additional cash infusion—$500,000 to $1 million a year—to better maintain and expand the Board of Health's databases.

Budget shortfalls, however, are not as contentious as the question of access. "The central issue is the refusal by Statistics Denmark to release personally identifiable CPR-related data," says epidemiologist Thorkild I. A. Sørensen of Copenhagen's Institute for Disease Prevention. The agency's rules, stricter than mandated by law, make accessing data a cumbersome process. If researchers want to link data from a health database to data from a demographic database, for example, they pay a steep fee for an appointment at Statistic Denmark's Copenhagen office, where they wait while a bureaucrat carries out the request. Researchers can't take home with them data coded by CPR, which constrains how they manipulate data at their institutions. Performing follow-up analyses that require linking data by CPRs means returning to Statistics Denmark and paying another fee.

Researchers argue that the benefits of entrusting them with the CPR outweigh the risk of compromising the identifying information. It's "better to meet concerns by tightening possible sanctions than to limit research that benefits society in general," says Sørensen. While the company deCODE's plan to create and mine an Icelandic health database has provoked heated debate in Iceland and abroad (*Science*, 11 February, p. 951), the database issue has aroused little concern in Denmark. In part that's because no one has suffered the embarrassment of having their medical records inadvertently released into the public domain: Researchers must strip CPRs from health data before publishing analyses, and they have no access to the names that go with the CPRs.

As the government committee considers their request, the researchers are forging ahead with new projects that aim to marry advances in genetics with the vast database resources. "The ability to track related individuals in the many different databases makes it possible to shed light on the complex interplay between familial predisposition and environment," says Melbye. Christensen's twins, for example, donate blood samples that are used to analyze genes implicated in aging. And in the Danish National Birth Cohort, 100,000 pregnant women and their babies are being recruited to donate blood and undergo physical exams during pregnancy. The emerging database may point to new connections between prenatal factors and congenital disorders, as well as chronic diseases that occur later in life. "In the future we can go back and analyze data concerning the mothers' health during pregnancy and test suspected genetic and nongenetic factors in blood," says epidemiologist Jørn Olsen of Aarhus University, one of the project's leaders. The data could be all the more useful, he says, if the current restraints on linking information across databases are lifted. Indeed, Christensen sees it as a moral obligation to exploit data gathered at great expense. "Would it not be unethical not to use it to improve the population's health and health care?" he asks.

–LONE FRANK

Lone Frank writes from Copenhagen, Denmark.

INTELLECTUAL PROPERTY

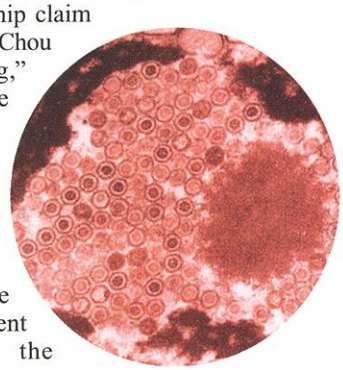
Patent Suit Pits Postdoc Against Former Mentor

A judge has thrown out a former postdoc's claim that her work was patented without her knowledge, ruling that the university owns her work so she lacks standing for a suit

Two years ago, biologist Joany Chou found herself in a postdoc's nightmare. She learned that what she considered her main accomplishment in 14 years of research on the herpesvirus—the discovery of a new gene—had without her knowledge been included in a patent by her mentor at the University of Chicago (U. of C.). She appealed to the university but was rebuffed.

Then came a mentor's nightmare. Seeking $25 million for the alleged misuse of her research, Chou took four defendants to court last July: her former professor and lab chief Bernard Roizman, a renowned herpes expert at the University of Chicago and member of the National Academy of Sciences; the university; the university's patent agency, the ARCH Development Corp.; and Aviron, a company co-founded by Roizman in Mountain View, California, which has rights to the disputed patent.

All the defendants have denied Chou's claims in court documents, and Roizman has argued that her contributions to the patented work did not merit co-inventor status. But in a ruling last month, Judge James Zagel of the federal court for Northern Illinois said the question of whether Chou or Roizman should get credit for the gene discovery is irrelevant. In an opinion that may be instructive for other postdocs, Zagel threw out Chou's inventorship claim on a legal point. Chou lacked "standing," Zagel said, because she was an employee of the U. of C. when the discovery was made. (The research was funded partly by the federal government and partly by the French firm Pasteur Mérieux.) The university's rules make it clear that it owns employees' inventions, Zagel noted, and this means that Chou never had any prospect of owning the patent. Zagel wrote: "One who



Infected cells. The $\gamma_1$34.5 gene is required for HSV to infect the central nervous system.

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claims no ownership of the patent has no standing to seek relief." Chou intends to appeal Zagel's decision.

Roizman declined to respond to questions. But his Chicago attorney, Paul Stephens, said in a faxed letter that "Chou's baseless allegations have been denied by the University of Chicago and by ARCH and by Dr. Roizman. Chou has already caused unnecessary upset and expense with her rash and unfounded charges. … So far, they have no legal merit. …"

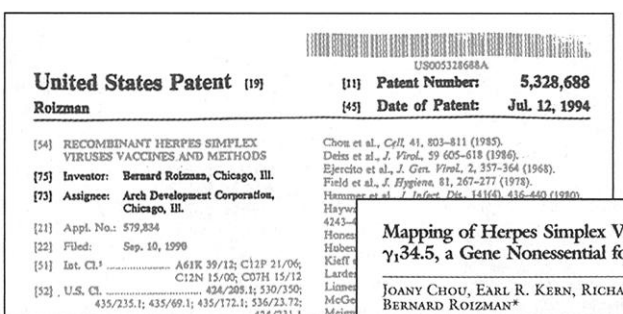
This bitter struggle holds lessons for postdocs and universities, says attorney Richard Aron Osman of Hillsborough, California, an expert on biotech property law. (Osman read the legal briefs and judge's decision at *Science*'s request.) Researchers "shouldn't be naïve," says Osman. "For better or worse, there is a lot of money surrounding biomedical inventions, and this has changed the relationship of trust that many students assume exists between them and their faculty advisers." He notes that most graduate students and postdocs have "limited knowledge of the patent system," and he wonders whether universities should provide an "ombudsman" to advise or advocate for student-inventors. This might forestall some litigation, he thinks.

The dispute began in 1997, Chou says, when she first learned of Roizman's patent. The previous year, Chou had left Roizman's lab after a disagreement with him. She had worked there as a graduate student and later as a $25,000- to $35,000-per-year postdoc. Chou first saw the patent, which had been awarded in 1994 (U.S. patent 5,328,688), by chance, she recalls, when a researcher came up to her as she was being interviewed for another job and "waved this paper at me." Chou says she was "devastated."

In 1990, Chou and Roizman co-authored papers on a key herpes simplex virus (HSV) gene known as $\gamma_1$34.5. They showed that deleting or blocking the $\gamma_1$34.5 gene blocks the virulence of HSV by making it unable to infect the central nervous system (CNS). Such mutant viruses can still grow harmlessly in the body. This "tame" form of HSV might be useful in an anti-HSV vaccine. Chou says she discovered the $\gamma_1$34.5 gene "by accident" when she was dissecting HSV under Roizman's tutelage in the 1980s. Not only was the gene novel, but some HSV researchers refused to believe it was real. Two well-known scientists recall how leaders in the field nearly came to blows at a meeting where a British scientist challenged the discovery. But Chou and Roizman stood by the results.

Today, some researchers are unsure how they would allocate credit on the patent, even though Chou and Roizman co-authored the key papers. Joseph Glorioso of the University of Pittsburgh says, "Chou's work was very well done, with a high degree of scrutiny by Bernard [Roizman], I'm sure." But it's "easily conceivable," Glorioso says, "that someone could be first author on a paper and not included on a patent."

Two other researchers who asked not to be named say they regard Chou as the gene's discoverer, although Roizman guided the research. A third, virologist Priscilla Schaffer of the University of Pennsylvania, Philadelphia, strongly agrees that Chou should get credit as a discoverer: "I was absolutely blown away when I found that Joany's name was not on that patent," she says. Schaffer argues that "it's very difficult" to separate intellectual contributions and benchwork in science. "Bernard may be saying that Joany had no intellectual input into this discovery, but I find that hard to believe. I think she has been done an injustice."



US005328688A

United States Patent [19]
Roizman

[11] **Patent Number:** 5,328,688
[45] **Date of Patent:** Jul. 12, 1994

[54] RECOMBINANT HERPES SIMPLEX VIRUSES VACCINES AND METHODS
[75] Inventor: Bernard Roizman, Chicago, Ill.
[73] Assignee: Arch Development Corporation, Chicago, Ill.
[21] Appl. No.: 579,834
[22] Filed: Sep. 10, 1990
[51] Int. Cl.[5] A61K 39/12; C12P 21/06; C12N 15/00; C07H 15/12
[52] U.S. Cl. 424/205.1; 530/350; 435/235.1; 435/69.1; 435/172.1; 536/23.72;

Chou et al., *Cell*, 41, 803–811 (1985).
Deiss et al., *J. Virol.*, 59 605–618 (1986).
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Mapping of Herpes Simplex Virus–1 Neurovirulence to $\gamma_1$34.5, a Gene Nonessential for Growth in Culture

JOANY CHOU, EARL R. KERN, RICHARD J. WHITLEY, BERNARD ROIZMAN*

The gene designated $\gamma_1$34.5 maps in the inverted repeats flanking the long unique sequence of herpes simplex virus–1 (HSV-1) DNA, and therefore it is present in two copies per genome. This gene is not essential for viral growth in cell culture. Four recombinant viruses were genetically engineered to test the function of this gene. These were (i) a virus from which both copies of the gene were deleted, (ii) a virus containing a stop codon in both copies of the gene, (iii) a virus containing after the first codon an

Authorship and inventorship. *Science* paper *(right)* and subsequent patent *(above)*.

Although Roizman declined to respond to questions, his filings with the Patent and Trademark Office (PTO) and legal briefs offer a glimpse of his position. When Roizman submitted a patent application in 1990 on a virus in which the $\gamma_1$34.5 gene was mutated and associated vaccines, the PTO examiner initially rejected it for several reasons, including that it seemed obvious. The examiner argued that one could easily combine papers by Chou and Roizman on the $\gamma_1$34.5 gene with a patent Roizman obtained in 1989 for a similar vaccine using a different gene. Combining this information—as any expert could do—would make the 1990 vaccine idea obvious, the examiner said. In a series of letters and personal visits, however, Roizman persuaded the PTO to reconsider.

Roizman argued in 1992, for example, that the $\gamma_1$34.5 discovery made this invention entirely novel: A virus with this mutation, he wrote, "exhibits significantly less virulence" than the mutation he had patented in 1989. Roizman also told the PTO that Chou's contribution to this improvement was not critical. In a sworn affidavit on 8 July 1993, he stated that he was the "sole inventor" and had directed the research in the key scientific paper. "While co-authoring the publication, Joany Chou is not an inventor of the subject matter reported therein," Roizman wrote.

Contesting this assertion last year, Chou gave the court a letter Roizman sent to the U. of C. molecular genetics department in May 1994 recommending her for promotion. In it, Roizman described Chou's research as "outstanding," specifically her "original and seminal work" on HSV. "Several years ago," Roizman wrote, "Joany discovered a hitherto unknown herpes simplex virus open reading frame," the $\gamma_1$34.5 gene. Roizman wrote that "in short order she made a series of deletions within the gene and demonstrated" that "deletion mutants are totally unable to grow in CNS of experimental animal systems even though the mutants do multiply in non CNS tissues." He concluded modestly: "There is significant interest in this gene and in the deletion mutants."

Neither Roizman nor the university informed Chou that a patent was pending on the $\gamma_1$34.5 gene discovery, Zagel noted. Nor did they inform Chou of the patent's issuance in 1994. Roizman's legal brief argues that as a mentor he was not "bound by an affirmative duty to discuss with Chou every patent application filed … to ensure that Chou had not been incorrectly excluded." Zagel agreed.

In 1996, Chou says, Roizman asked her to leave his lab because he considered her disruptive and because she had filed a supplemental grant application as an independent investigator, but hadn't cleared the text with Roizman. Chou has been on her own since 1997.

University officials declined to discuss the case. But press officer John Easton provided a brief statement saying that the university's rule is that all researchers should be "accorded full credit for their work" and that outside attorneys help allocate credit properly. The note states that Chou is listed as an inventor on other patent applications and on a 1998 patent for a method for screening proteins. University officials have reviewed Chou's allegations carefully, the statement says, and "concluded that Dr. Chou has been treated fairly."

One irony in this dispute is that so far the patent has produced no vaccine, and Chou, by her own estimate, has spent $200,000 contesting it. **–ELIOT MARSHALL**

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