ALZHEIMER'S RESEARCH

# Allen Roses: From 'Street Fighter' to Corporate Insider

If science is a battleground of ideas, one of its most uninhibited warriors is Allen Roses. Last June, in a characteristic gibe at the establishment, the Duke University neurologist told a Senate subcommittee that his competitors had blocked him from getting grants from the National Institutes of Health (NIH) for his research on Alzheimer's disease. "We have been blackballed ... because of dogmatic belief systems of narrowly focused scientists" who review grant proposals, he complained. Peer review, he added, is skewed "by a few nonobjective, overopinionated, mutually anointed experts."

To colleagues and competitors who have interacted with him over the years, the performance was vintage Roses. He likes to portray himself as a "lone wolf," says one high-ranking scientist. But less than 2 weeks after that hearing, Roses was suddenly transformed from self-described outsider to consummate insider: On 17 June, the British-based pharmaceutical giant Glaxo Wellcome named Roses head of its worldwide genetics research efforts. "I went from being somebody who couldn't get a grant at NIH to someone who had the resources to do what I think needs to be done," Roses said recently.

Within weeks of his new appointment, Roses, 55, established himself as a major player in some of the hottest issues in genetics. He has formed collaborations with clinicians in Europe to try to untangle the complex genetics of common multigene diseases such as asthma, stepped up Glaxo's work on gene mapping, launched a project to sequence 4 million bases on chromosome 19 in part to see how fast the company's scientists could do it, and begun a collection of single nucleotide polymorphisms—single-base variations in DNA that could be useful in identifying new disease genes.

Roses's new position makes him a member of an elite group of ex-academics running big industrial genetics programs, including Peter Goodfellow, who moved from Cambridge University to SmithKline Beecham of London in 1996, and Tom Caskey, who left Baylor University for Merck & Co. Inc. of New Jersey in 1995. Roses now oversees a $50 million genetics budget, part of Glaxo's $2 billion annual R&D effort. And he says he is awed by the resources his company can bring to bear on research projects.

In recent interviews with *Science*, Roses discussed his goals for genetics research at Glaxo and his battles with skeptics about his Alzheimer's work. Those battles are legendary in the field, and they say a great deal about the drive and bulldog approach that Roses brings to his new job. In Roses's view, the Alzheimer's field is "the most cutthroat place" because it has all the competitiveness of molecular genetics with big financial stakes thrown in. Roses's colleagues would add, however, that he has done his share to make it cutthroat.

### The making of a maverick

Roses "seems to thrive on controversy," says Peter St. George-Hyslop, a geneticist at the University of Toronto. And Richard Mayeux of Columbia University, a neurologist who has co-authored articles with Roses, finds that "people tend to get their dander up when they talk to Allen." Pathologist John Trojanowski of the University of Pennsylvania says, "Allen has a way of stirring up controversies. ... But it's not something we should quash; it's good to have debate." Roses would agree: "I have been personally called a number of things," he said at the hearing last year before the Senate subcommittee on aging. Among "the more favorable," he said, are "maverick" and "street fighter." He doesn't mind playing the adversary, though, for as he says: "I may be unpopular, but I'm not wrong." Indeed, even his critics agree that Roses made a major contribution with the discovery of a gene that increases a carrier's risk of developing the common, late-onset form of Alzheimer's—a discovery that was initially ignored by many in the field.

SAM KITTNER

**"I may be unpopular, but I'm not wrong."**

**—Allen Roses**

According to Roses, skepticism about his work traces back to the early 1980s, when he became director of the Alzheimer's Disease Research Center at Duke University, "having never published a paper on Alzheimer's disease." As chief of neurology, Roses had been doing research on myotonic muscular dystrophy. He got the job, he explains, because his dean came to him one day in 1984 and asked him to apply for one of the new center grants being offered by NIH's National Institute on Aging.

Roses began studying Alzheimer's-prone families to find chromosomes important for the disease, in collaboration with Duke colleagues Margaret Pericak-Vance, Donald Schmechel, Warren Strittmatter, and Ann Saunders (who became his wife). In 1987 and 1988, other groups had begun to publish papers on hot regions of chromosomes 21 and 14, where candidate genes for Alzheimer's were likely to be found. In 1990, the Duke group reported linkage to an area of chromosome 19 for the common, late-onset form of the disease. But, says Roses, "we had no competition because nobody thought [chromosome 19] was real."

John Hardy, a geneticist formerly at Imperial College, London, and now at the Mayo Clinic in Jacksonville, Florida, agrees that "the field made a mistake" in overlooking this early finding. Hardy considers himself a competitor and a critic of Roses, although he adds, "I enjoy grappling with Allen." But he concedes that he didn't see the importance of Roses's data soon enough. "For about 3 years, Allen was telling us there was something important on chromosome 19," Hardy says. "But everyone basically ignored him—even, surprisingly, those of us who had within our own data sets evidence of genetic linkage on chromosome 19." He credits Roses with the "courage to push ahead," adding that Roses is an "in-your-face type of guy" who carried through, in part, "just to show us we were wrong."

As the Duke team tried to nail down evidence of a gene on chromosome 19, Roses got into behind-the-scenes clashes with competitors. The noisiest row was with Hardy, who recalls that "I had to hold the phone a few feet from my ear" when Roses called one day in 1991, because Roses had gone "absolutely ballistic." Roses was angry about not being credited in a paper of Hardy's in press at *Nature* reporting that a mutation in a gene located on chromosome 21 is linked to a rare, early-onset form of

# The Alzheimer's Gene Puzzle

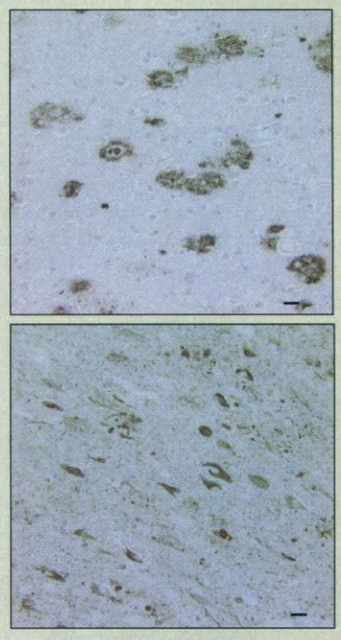
Six years ago, Allen Roses and his team at Duke University stunned their peers when they said they had found a connection between a gene that helps the body metabolize fats (the apolipoprotein E gene, or *APOE*) and Alzheimer's disease. Many were skeptical. But the *APOE* discovery has held up, and it looks like a major find. It is the only common genetic factor known to be involved in Alzheimer's, a disease that afflicts roughly 4 million people in the United States.

The risk associated with *APOE* has been confirmed many times since 1992. Studies have shown that people who die of Alzheimer's disease are more likely than non-Alzheimer's patients to carry a particular form of the *APOE* gene. For example, whites 60 to 80 years old with two copies of the *E4* allele are nine times more likely to get the disease than those who don't carry it. But almost everything else about *APOE*'s role remains obscure. Many theories are in contention.

One of the most controversial ideas was proposed by Roses and his colleague, neurologist Warren Strittmatter of Duke. Shortly after finding the *APOE* connection, they suggested that "normal" *APOE* protects the brain. They argued that the most common of *APOE*'s three genetic forms—the *E3* allele—produces a protein that binds to another protein called tau, and that together they maintain the structure of neurons. But the *E4* allele, according to this theory, codes for a protein that doesn't bind well with tau, causing neurons to develop the tangled fibrils found in Alzheimer's brains. That would explain why a person with one *E4* allele would have a moderate risk, and a person with two *E4*s would have a high risk of getting Alzheimer's. Very few scientists have been persuaded, however.

"I haven't seen any data that support physiological relevance [for Alzheimer's] of an interaction between tau and *APOE*," says Rudy Tanzi of Massachusetts General Hospital in Boston. Research administrator Marcell Morrison-Bogorad of the National Institutes of Health's (NIH's) National Institute on Aging agrees that Roses and Strittmatter "haven't convinced many people as of yet." Indeed, Strittmatter's NIH grant hasn't been renewed.

Many Alzheimer's disease researchers are betting on a different mechanism, says Sam Sisodia of the University of Chicago, recent winner of a Metropolitan Life award for Alzheimer's research. They are interested in how genes contribute to the buildup of a telltale pathological feature of brains from Alzheimer's patients—a waxy plaque called amyloid. Sisodia points out that three other Alzheimer's genes, all linked to early-onset forms of the disease, are involved in the amyloid process. Mutations in these three—the presenilin 1 and 2 genes and the amyloid precursor protein (*APP*) gene—are rare but potent. People who carry them are virtually certain to get the disease, yet they make up less than 5% of all Alzheimer's patients. Sisodia thinks it significant that "all point to the same idea—that amyloid is an essential feature of the disease."



PROVIDED BY THE LAB OF DRS. V.M.-Y. LEE AND J.Q. TROJANOWSKI

**Brain proteins.** Alzheimer's brains stained to show β amyloid *(top)* and tau.

But Roses dismisses amyloid as "scar tissue" resulting from the neuronal damage, not a cause of Alzheimer's. For evidence, he cites a study by Brad Hyman's lab at Massachusetts General Hospital that examined mice genetically engineered to carry the mutated *APP* gene. These animals' brains become clogged with amyloid, but their neurons remain healthy. To Roses, this indicates that "amyloidologists" have been looking at consequences, not causes, of the disease. Sisodia calls this view "extreme."

But there may yet be hope for common ground in Alzheimer's research. Many scientists agree with Gerard Schellenberg of the University of Washington, Seattle, who says work done in the past few months by researchers in Steven Paul's lab at Eli Lilly & Co. in Indianapolis is "cool and exciting." What makes it exciting, Schellenberg says, is that it suggests that *APOE* and *APP* might interact.

Paul's group crossed two strains of genetically engineered mice—one in which the *APOE* genes are "knocked out" and another in which the human *APP* mutation has been inserted. Normally, the *APP* mutation causes mice to develop dense amyloid plaques starting at 4 to 5 months, says Paul. But the *APOE*-deficient hybrids in his lab developed no plaques, even after 22 months. As an indication of how surprising this was, Paul says he lost money on the experiment: "I had a bet we would see more amyloid in the *APOE* knockouts, but instead we saw none," he recalls. In a follow-up experiment, Paul's group crossed *APP* mice with mice that had just one gene for apolipoprotein E. These mice developed amyloid plaques, but at half the speed or density of animals with two *APOE* genes. This clearly suggests, Paul says, that amyloid deposition depends on apolipoprotein E. Next, Paul's group wants to see what happens to mice engineered with human *APOE* alleles (*E2*, *E3*, and *E4*).

Ironically, Paul notes, this experimentation comes full circle to ideas explored years ago at Duke. In 1993, Roses, Strittmatter, and Donald Schmechel reported a study of Alzheimer's patients that showed a correlation between the number of *APOE4* genes and amyloid deposition, suggesting *APOE4* was involved in the amyloid phenomenon. That was before Roses embraced the tau theory and shunned the "amyloid club." But Paul says those old data and the mouse data from his lab "fit together very nicely." **–E.M.**

Alzheimer's disease. It was the first gene to be associated with Alzheimer's.

"I went berserk," Roses says, when "we received an anonymous fax from [London's] Paddington Station" of a prepublication proof of the *Nature* article. It included evidence for the new gene from a Duke Alzheimer's family, but did not include the Duke researchers as coauthors. Hardy, who now agrees this was wrong, explains that Roses had shared his family material 2 years earlier as a challenge or "act of bravado," not in collaboration. Because Roses had declared himself a doubter on chromosome 21, Hardy felt he should not be a coauthor. Hardy also says a university patent lawyer instructed him to limit knowledge of the discovery until a patent had been filed. "I was younger then, and I believed lawyers," Hardy explains, so he kept the list of authors and proofreaders short. Finally, Hardy felt that British science deserved a turn in the limelight.

Roses demanded to be included, Hardy recalls, but he turned Roses down. Soon Duke's lawyers called. Then NIH's lawyers called. Under pressure, Hardy says, "we had to put Allen's and Peggy's [Pericak-Vance's] names on the paper." The incident "caused a

rift" in the community, Roses says, and led to a "polarization of the field."

The next year, 1992, Roses says he was "fuming" again—this time over a paper published by Gerard Schellenberg of the University of Washington, Seattle, reporting a linkage to chromosome 14 among a larger number of families. They were prone to another rare, early onset form of Alzheimer's disease. Roses was miffed that the Seattle group had also used Duke's material with less credit than he thought was due. Roses says he went to a meeting of Alzheimer's center directors in October 1992 in a reckless mood.

There, he announced that he and the Duke team had found what they were looking for on chromosome 19: the first gene associated with late-onset disease, the form that affects the majority of patients. This was the apolipoprotein E (*APOE*) gene, which codes for a molecule previously identified as a transporter of lipids and never suspected of playing a part in Alzheimer's. Roses's announcement got little notice, however.

About 8 months later, after another public talk, Roses finally made a splash. He remembers it well: "On June 7, 1993, my life changed," he says, pointing to a framed article on that date from *The Wall Street Journal*. A front-page story credited the Duke team with finding *APOE* and possibly opening a new path for Alzheimer's studies. The *APOE* connection was startling because, unlike other gene discoveries, it linked to the common, post–60-year-old form of Alzheimer's that afflicts the overwhelming majority of the 4 million U.S. citizens with the disease. To put this in perspective, Roses says, consider that the most common early onset Alzheimer's mutation, the one on chromosome 14, affects "fewer than 100 families in the entire world," and that mutations on chromosomes 21 and 1 together affect fewer than 25 families. In contrast, the risky form of *APOE*—the *E4* allele—is so common it's not called a mutation. Among Caucasians, it turns up on all chromosomes with a well-established frequency of 15%. Roughly 30% of the population carries at least one *E4* allele, and the 2% who have two copies have a high risk of getting Alzheimer's.

After that, Roses says his group was no longer viewed as "harmless," because "we got the publicity that everybody else wants." In a reversal of the usual pattern, he and his colleagues later published their results in scientific journals, including *Science* (13 August 1993, p. 921). Today, Roses still celebrates that triumph with a license plate on his sporty blue BMW that reads, "APOE19." His wife Ann Saunders, a co-author on much of the *APOE* work, drives a BMW with a plate that says, "ROSES19."

In 1993, however, the controversy over *APOE* was just beginning. In November, Zaven Khachaturian, then at NIH's National Institute on Aging and a supporter of Roses's work, invited Roses to speak at an NIH-sponsored press conference in Washington, D.C. Khachaturian has written that he felt the tension growing between Roses and his peers during the session: "Skeptics were hanging from the rafters," Khachaturian recalled in the July/August 1997 issue of *The Sciences*, and "leading medical investigators in the audience questioned Roses's research methods and hooted that his work was too lame even for a pilot study."

Among the skeptics was Rudy Tanzi, a geneticist at Massachusetts General Hospital in Boston. He has questioned whether it was even correct to call *APOE* an Alzheimer's disease gene, because it didn't appear to cause the disease directly but increased the risk for it, just as cholesterol increases the risk of a heart attack. Many people who inherit two copies of the *E4* allele live into their 80s without getting the disease, and many who do get Alzheimer's do not have the *E4* allele, Tanzi points out.

More recently, Tanzi has expressed doubts about a report by the Duke researchers last October that they had found linkage to a new Alzheimer's risk locus on chromosome 12. Both Tanzi and Ellen Wisjman of the University of Washington, Seattle, say they do not find this linkage in families they've studied. But Tanzi does believe there is an important Alzheimer's gene on chromosome 12—just not where Roses's group says it is. Tanzi is careful about voicing criticism of Roses these days, however, saying only that since he expressed early doubt about *APOE*, "Allen and I have not been on good terms."

### Blackballed?

Although the *APOE* finding was quickly confirmed, the experts have continued to debate how *APOE* might cause disease. Roses and his Duke colleague Strittmatter argue that beneficial versions of *APOE* (the *E2* and *E3* alleles) generate a protein that protects nerve cells, while the *E4* allele does harm by producing too little protein (see sidebar on p. 1002). Roses has been searching for the beneficial effects of *APOE2* and *APOE3*. (A recent study at Washington University in St. Louis suggests that *APOE3* may be a nerve growth factor—see Random Samples, p. 1013.) The Duke team's search is now being supported by Glaxo, which would like to market *APOE*'s good qualities, if any can be found.

But many other leaders in the field have been trying other approaches, focusing on harmful proteins produced by early-onset genes. They believe, as Tanzi explains, that it is "more efficient" to explore the disease by looking at harmful mutations that seem certain to be associated with the causes of disease, rather than looking at *APOE4*, which is only a contributing factor. They are exploring the idea that mutations on chromosome 21 and 14 increase amounts of a protein (β amyloid) that forms plaques in the brains of Alzheimer's patients. But Roses regards amyloid as "a scar," not a cause of disease. He is unimpressed by the "cabal" of amyloid experts.

It was this opposition to the conventional wisdom on β amyloid that, Roses claimed in his Senate testimony, led to his being blackballed by NIH peer-review committees. Asking to remain anonymous, one researcher claims that the performance was carefully calculated: "It is typical of Allen to bludgeon the system to get what he wants." This scientist claims that NIH officials responded to pressure from Roses, funding a Duke proposal despite poor marks in peer review. But Roses says that although some members of the center have pieced together support, "Allen Roses as a principal investigator had no grant from the NIH after the LEAD award [a $5 million, 7-year grant] lapsed" in 1995.

**GENES ASSOCIATED WITH ALZHEIMER'S DISEASE**

| Gene | Chromosome | Function | Prevalence | Published | Team |
|---|---|---|---|---|---|
| *APP* | 21 | amyloid protein mutation | <1% | 1991 | Goate, Hardy *et al.* |
| *APOE4* | 19 | risk factor, function debated | 30% | 1992 | Roses *et al.* |
| *PS1* | 14 | mutation, function unknown | <1% | 1992 | Schellenberg *et al.* |
| *PS2* | 1 | mutation, function unknown | <1% | 1995 | St. George-Hyslop *et al.* |
| ? | 12 | risk factor | ? | — | Pericak-Vance *et al.* |
| ? | 12 | risk factor | ? | — | Kang, Saitoh *et al.* |

### New plans

It was partly because of this academic sniping, and mainly to keep his research going, Roses says, that he left Duke last summer after 27 years and took the job at Glaxo. He and Pericak-Vance had been talking to venture capitalists about starting their own genomics company, which they were going to call Cerberus. The negotiations were tedious and demeaning, Roses recalls. Then, in May, the former Duke biochemist who directs research for Glaxo, James Niedel, called and invited Roses to dinner. The company wanted "somebody who's not going to sit on the fence," says Roses, adding, "I don't think

## A Clash Over Testing for Alzheimer's Disease

Last fall, when a group of experts argued against widespread use of a diagnostic test for Alzheimer's disease devised by neurologist Allen Roses and his former colleagues at Duke University, Roses hit the roof. He fired off a salvo of e-mails to the group's leader, attorney Henry Greely, accusing the panel of using "loose analysis" and "misinterpreted data" and "repeating a lie" that physicians are already highly skilled in diagnosing Alzheimer's. Roses "is not a tactful man," says Greely, measuring his words carefully.

This clash focuses on a test for an allele of the apolipoprotein gene, known as *APOE4*, that is a risk factor for developing Alzheimer's late in life (see p. 1002). Roses had suggested that doctors could give the test to demented people to make their diagnosis of Alzheimer's more certain. But the panel, sponsored by Stanford University's Center for Biomedical Ethics, issued a draft opinion in October stating that "genetic testing for [Alzheimer's disease] is not appropriate for most people." It said that testing for rare Alzheimer's genes—dominant mutations that almost invariably lead to early-onset disease—"may be appropriate" in the small number of families at risk for these genes. But for the vast majority who get the disease later in life, "neither predictive nor diagnostic genetic testing for susceptibility genes (e.g., *APOE*) should be encouraged at this time."

The Stanford group noted that a recent study of autopsy data found that physicians using only clinical criteria had correctly diagnosed Alzheimer's in 85% to 87% of patients by the time of their death. A genetic test may offer a modest improvement, Greely says, but given the lack of any good therapy for the disease and the harm that knowledge of *APOE* status might do to family members, the case for widespread use of the *APOE* test was "not compelling." Greely has not released the final report, which has been submitted for publication.

Several earlier reviews had come to similar conclusions about testing for *APOE*, and some skeptics take an even stronger line. Peter Whitehouse of Case Western Reserve University in Cleveland points out, for example, that data published in March by Ming-Xin Tang, Richard Mayeux, and colleagues at Columbia University indicate that African Americans and Hispanics do not exhibit the same *APOE*-related Alzheimer's risk that whites do. Whitehouse says *APOE* testing may be useful, but only for "those academic white people who volunteer for research studies" and not for patients "an average primary care practitioner would see."

Roses is unyielding. He claims that physicians who rely on traditional criteria to make a diagnosis identify Alzheimer's in only 60% to 70% of patients during an initial visit. Testing for *APOE4*, he claims, could raise that accuracy rate to 95%. "From a practical point of view," he says, it makes a big difference for a physician to be able to diagnose a patient correctly with 95% confidence on the first visit. If nothing else, Roses argues, knowing that a diagnosis of Alzheimer's is correct would give comfort to patients' families. He adds that recent research on minority patients is only a "first step" in analyzing the *APOE* risk in these groups, representing a less than ideal sample. Mayeux himself says that his findings do not reduce the importance of *APOE4*; they merely signal that other genes may be more important for minorities.

In a different realm, Roses insists that the *APOE* test has already proved its worth: "Every major drug company is stratifying its drug studies with *APOE*," focusing clinical trials on patients most at risk for Alzheimer's. **–E.M.**

anybody's ever accused me of that." When Niedel agreed to commit $3 million to the Duke research lab and supported his strategic plans, Roses says, he accepted the job.

Roses quickly set about creating what he calls a "network of clinicians" to do on a big scale, for many different diseases, what his colleagues at Duke have been doing for Alzheimer's. These extramural partners, Roses explains, will provide data and clinical material to Glaxo in its hunt for disease-related genes. The material will remain with the physicians, but Glaxo will patent key discoveries—including genes—and manufacture drugs based on them. The analyses will be done at Duke, among other places. The first network is based in Europe and focused on asthma. Others will look at cardiovascular disease, depression, schizophrenia, inflammatory bowel disease, dermatitis, and susceptibility to infectious agents.

Roses intends to help Glaxo master the newest fashion in drug development, called "pharmacogenomics." It involves building up detailed indexes of variations in human genes (like the three alleles of *APOE*), using these indexes to scan the genomes of patients or volunteers. With new bioelectronic technology, it may be possible to gather up such "genotypes" at relatively low cost. Companies like Glaxo aim to conduct statistical comparisons of these data to look for disease-linked genes. The beauty of this approach, if it works, is that it may yield results without the need for expensive, time-consuming collection of family data. And it may enable researchers to find genes whose effects are so subtle they might not turn up in traditional studies.

To test the company's ability to build the requisite genomic maps for this enterprise, Roses ran a "proof of principle" exercise last summer. He asked the intramural Glaxo staff to sequence a 4-million-base segment of human DNA centered on the *APOE* gene on chromosome 19. Glaxo's European staff began sequencing north of *APOE* on the genome, and the U.S. staff went south. "I couldn't believe it," Roses says: "They were finished by Christmas." As part of the task, they identified 114 points in this region where different people's DNA differs by just a single base—so-called "single nucleotide polymorphisms," or SNPs. Many are spaced less than 1500 bases apart, Roses says, making them useful for identifying the exact location of genes.

Roses thinks that, by robotizing SNP collection and renting sequencing capacity, Glaxo would be able to cull SNPs from 60% of the genome "very, very quickly," perhaps in 2 to 3 years. The company is willing to donate the SNPs to the public, after patentable genetic data have been extracted and patents filed.

As proposed by other companies like Genset of Paris, Glaxo will also use SNP maps to genotype and "bar-code patients" in clinical trials, according to Roses—for example, selecting only those with an *APOE4* allele for participation in Alzheimer's drug trials. Eventually, he thinks, it will be possible to sort patients according to their response to many drugs. The immediate value, proponents say, will be to focus clinical trials on people most likely to benefit. If "nonresponders" and misclassified patients can be screened at the outset, some say the cost of clinical trials could be reduced by as much as 30%.

After a period of finding his way around what Roses calls "my first new job in 27 years," Roses seems to be enjoying himself. "I've been fighting all my life, like a bow cutting through ice, and I've been getting a little worn down," he said last year. Working in industry, he claims, has been "refreshing." The downside, he told attendees of a Glaxo staff meeting last year, is that he gave up "a nice, cushy job" with tenure in exchange for "one of those contracts where you're here today, and the next day, you're gone." Gone, but surely not forgotten, if his impact on Alzheimer's research is any guide.

**–Eliot Marshall**