ily reflect the increased blood supply at the site as any specific TIL homing.

Gene-modified TIL cells that don't localize not only have no therapeutic value but also may end up in the liver, where the TNF, which is toxic, could be a problem. So far, Rosenberg says, none of the nine patients he has enrolled in the study have shown any signs of toxicity. But with the relatively low levels of TNF the TIL cells were secreting, said Levy, that result is not surprising. And he questioned if it was "worth it" to continue toxicity testing "given these secretion and localization [levels]."

Hoping to answer some of these concerns, Rosenberg presented data to the board that showed that treating patients with cyclophosphamide, a chemotherapeutic drug, apparently doubled the likelihood of their TIL cells ending up at tumor sites. But the trial was unrandomized, a point the board noted in its criticism. "It was very clear that Rosenberg couldn't provide data to relieve [the DCT board's] anxieties," Wivel says. In response, Rosenberg announced that he intends to conduct a fully randomized trial on the influence of cyclophosphamide on TIL localization, which could finally resolve the point.

The board agreed to consider those data when they become available, but it was unwilling to lend its support to continuing the TNF/TIL trial based on the data it had seen so far. "When I go through your numbers, I come up very short of an effective gene therapy," Levy told Rosenberg at last week's public meeting. "I think it might be better to wait" for better preclinical data before continuing with the trial, he said.

NIH cancer researcher Michael Blaese, whose team collaborated with Rosenberg on many of the initial laboratory experiments, says that TNF/TIL initially looked like a good bet, but that difficulties in the approach soon arose. "The first experiments [with gene-modified TIL cells] were better than the later ones," he says. "In hindsight, the initial data were spotty. The initial promise they generated in the lab couldn't be maintained. It was really hard for us to get any cytokine genes expressed in TILs."

Nevertheless, Blaese defends Rosenberg's risk-taking: "Steve's controversial, but he's been remarkably effective at bringing new [technologies] to clinical trials. I hate to see him knocked for it. It's too bad that the [DCT] committee had to publicly slap him."

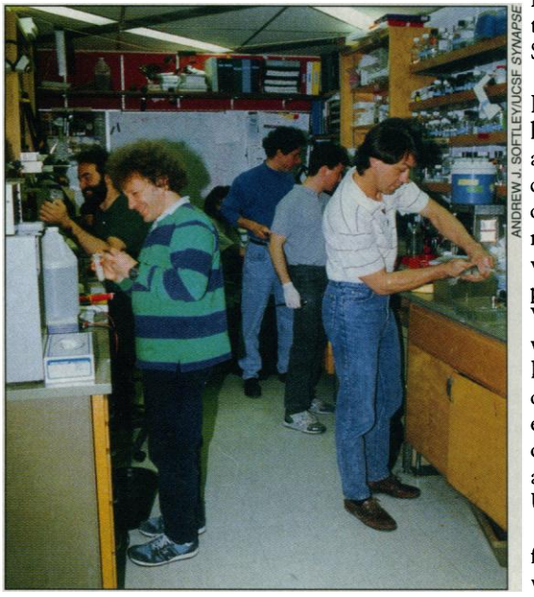
Yet Blaese is not surprised that Rosenberg is now being challenged for his aggressive approach. "Steve has his passionate supporters and his equally passionate detractors," he says. As Wivel sees it, Rosenberg is a victim of the publicity he has generated. "You have a choice which path you take," Wivel says. "If you chose high visibility, you've got to take your lumps."

–Christopher Anderson

RESEARCH INSTITUTIONS

Space Woes Begin to Take a Toll at UCSF

The University of California, San Francisco (UCSF), is legendary for its rapid rise to a place among the world's top biomedical research institutions. Considered average only 20 years ago, it now commonly ranks first or second among U.S. medical schools in annual grant support from the National Institutes of Health, and handily competes with the likes of the Massachusetts Institute of Technology, Stanford, and UC Berkeley for the best graduate students and junior faculty. But this thriving campus is also legendary for something else: its space problem. Hemmed in by an agreement not to expand at its main site at Parnassus Heights in San Francisco, and stymied by neighborhood activist groups in its efforts to grow elsewhere in the city, UCSF finds itself with a faculty crowded together like sardines in a can.



ANDREW J. SOFTLEY/UCSF SYMAPSE

Elbow to elbow. Researchers work together in cramped quarters in a typical laboratory at UCSF.

Now, faculty members and administrators are worried that their cramped quarters might be endangering the university's top-notch reputation. The reason: Three key faculty members have recently accepted offers from other institutions, at least partly because of space problems. Cell biologist Marc Kirschner is departing for Harvard and human geneticists Rick Myers and David Cox are moving to Stanford. Concerned UCSF faculty and administrators took their case to the UC regents on 18 February, asking for support in finding room to expand. Without space relief, they warned, UCSF's faculty and reputation are at risk of slipping away.

The current departures are no small loss to UCSF. Kirschner, a leader in cell biology, has been instrumental in recruiting outstanding young cell biologists to the faculty. He goes to Harvard Medical School next fall to chair a new cell biology department there. The widely respected Cox and Myers direct a Human Genome Project mapping center, which will move with them to Stanford this month.

Kirschner came to UCSF from Princeton in 1978 during a wave of hiring that included such appointments as biochemist Bruce Alberts (now president-elect of the National Academy of Sciences) from Princeton, yeast geneticist Ira Herskowitz from the University of Oregon, and then assistant professors Keith Yamamoto and Harold Varmus (who won a 1989 Nobel Prize with his UCSF colleague Michael Bishop). Sharing a philosophy of cooperation and minimal hierarchy, the evolving group created the spirit of collegiality, irrespective of both rank and department boundaries, for which UCSF is now known.

But while that community was forming, a decision was made that would constrain its future. Expansion of the Parnassus campus had sparked a lawsuit by neighbors over traffic and congestion, and that led to a promise from the UC regents to limit growth at Parnassus to 3.55 million gross square feet—a size it had almost reached when the promise was made in 1976.

Thus began a phase of decentralization, in which the university farmed out programs to other sites. The most notorious and ill-fated of those satellite sites was a 360,000-square-foot office building in the Laurel Heights district, a few miles from Parnassus Heights, which was purchased in 1985 as a new home for the school of pharmacy. When neighborhood residents learned that research labs were part of the plan, they filed lawsuits that kept the pharmacy school from moving in, tightening the vise even more on the research labs at Parnassus Heights (*Science*, 11 March 1988, p. 1229).

"We outgrew [the size limits on the Parnassus campus] 10 years ago, and we have just become more and more cramped," says neurobiologist Michael Stryker, who came to UCSF as an assistant professor in 1978. Adds another faculty member, who requested

anonymity: "My lab is crammed as hell. It's dangerous." While there are a handful of larger labs on campus supported by the Howard Hughes Medical Institute or foundations, many full professors make do with 1200 to 1500 square feet—less than starting faculty get at most top universities. Some have gone to heroic lengths to eke out room. Kirschner is one of several who have at times turned their offices into lab space. And toilets have become an endangered species. It's common, says vice chancellor for planning Bruce Spaulding, for a faculty member to decide that a bathroom could be reduced from four stalls to two, and come up with a proposal to knock a hole through a wall at the cost of $1,000 a square foot, just to add 80 square feet to a lab. "We have closed bathrooms, and cut bathrooms in half. That's an indication of just how bad it is," he says.

Ironically, say some faculty, limited space may help maintain the community atmosphere that draws faculty to UCSF and keeps most of them from leaving. "Part of the reason people don't have empires is that there is no place to put one," says Stryker. Crowding also encourages interaction, he adds, as it did for him a few years ago, when his lab needed to use a new technique. "I had enough grant money to buy the [necessary] equipment, but I had nowhere to put it," he says. "So we had to do the experiments in Zack Hall's lab. We really learned a lot from rubbing elbows with those guys." But, Stryker adds, when elbow room gets too cramped, the impact on research is negative. Herskowitz, who chairs the Department of Biochemistry and Biophysics, agrees that UCSF has reached that point. "I would like to see the equivalent of a 5% to 10% increment of space at Parnassus Heights" he says, "just to keep the research healthy."

A key part of that prescription for health is space for junior faculty members to grow into. "We have continued to be able to hire first-rate junior faculty," says physiology chairman Zack Hall, "but in 4 to 5 years, as they prosper, they need more space. That is a critical junction." Each time there is a scramble for room, which Hall compares to "solving one of those little number puzzles that have only one open square." And the worry is that the solution will not compete with offers from other universities. The university has generally managed to "dodge the bullet," says Hall, "but it's a balancing act each time."

One case in which UCSF didn't dodge the bullet was that of Myers and Cox. Herskowitz, who also heads the genetics division, blames the space crunch directly for their departure to Stanford. When Myers arrived in 1986, there were plans to use laboratories vacated by the pharmacy school to create contiguous labs for Myers, Cox, and several yet-to-be-hired human genetics colleagues. But with Laurel Heights stalled, Myers and Cox remained in scattered quarters, without the colleagues they had expected. "We lost two tremendous young people because we didn't have the space," says Herskowitz.

Myers and Cox agree that space was a factor in their decisions to leave. They wanted to be part of a human genetics program like the one Stanford is building, says Myers. UCSF wanted to put together such a program, he adds, "but their hands are completely tied. You can't build programs if you don't have space." Kirschner says that while space concerns were "frustrating" and an energy drain, they weren't the only factor in his departure. He says he couldn't pass up the chance to chair a brand new department with multiple new positions, and to participate in building, at Harvard, an interactive community like that at UCSF.

Long-term relief for the frustrations expressed by Kirschner and others may be accompanied by its own set of frustrations: Administrators say the regents are unlikely to break their self-imposed space-ceiling at Parnassus Heights, meaning any growth will have to take place elsewhere. A faculty committee has recommended the creation of a second full-sized campus in or near San Francisco, an idea that is anathema to many faculty because it would cleave the UCSF community. But Spaulding says the split could be designed in a way that would keep collaborating groups together. The idea has not yet been formally proposed to the regents, and even if they accept it, building wouldn't begin before 1997 or so. Until then, departing geneticist Cox suggests UCSF may have to consider what many on the campus find unthinkable—limiting the areas in which it pursues excellence. Trying to do everything with limited space, he says, is "like sitting down to five Thanksgiving dinners." You may have room to eat one, but then you can only taste the others.

–Marcia Barinaga

NEUROBIOLOGY

Gene Linked to Lou Gehrig's Disease

Scientists have just taken a big step toward understanding the cause of Lou Gehrig's disease, one of the most devastating nerve degenerative diseases. A large team of researchers, led by Robert Brown Jr. of Harvard's Massachusetts General Hospital and Robert Horvitz, a Howard Hughes Medical Institute investigator at the Massachusetts Institute of Technology, report in the 4 March *Nature* that they've identified the gene that causes a hereditary form of the condition, which also goes by the name amyotrophic lateral sclerosis (ALS). While most ALS cases—approximately 90%—are apparently "sporadic" and not caused by an inherited gene defect, all the patients have such similar symptoms that researchers are hopeful that what they learn about hereditary ALS will also apply to the sporadic form, possibly leading to new therapeutic strategies that will help both. "It's a very important finding," says neurobiologist Donald Harter of the Howard Hughes Medical Institute. "It's one of the first handles we've had on the genetic basis of ALS."

"It's one of the first handles we've had on the genetic basis of ALS."
–Donald Harter

The researchers identified the gene, which encodes an enzyme called Cu/Zn-binding superoxide dismutase, after first finding about 2 years ago that the gene defect in some families with hereditary ALS maps to the long arm of chromosome 21. Among the few genes already mapped to that region, the superoxide dismutase gene seemed a reasonable candidate for the site of the ALS defect, says Horvitz. Superoxide dismutase helps cells get rid of superoxide free radicals, which can be produced by a variety of oxidative reactions and are extremely toxic, although it can also help generate other types of free radicals. If the enzyme were abnormal, free radicals might well build up, causing the death of the motorneurons, the nerve cells affected in ALS. This relentless neuronal degeneration kills in about 3 years on average.

In the current work, the researchers have shown that the superoxide dismutase gene is indeed mutated in patients, but not in unaffected individuals, in 13 different ALS families. "The implication is that high levels of free radicals are responsible [for ALS] at least in these families, and perhaps beyond," says Horvitz. Both he and Brown caution, however, that they do not yet have direct proof for this, even in patients known to have a defective superoxide dismutase, let alone those with sporadic ALS.

But if high free radical levels are involved, then it might be possible to treat or prevent ALS with compounds that can detoxify the radicals. These might include vitamins E and C, says Brown, although he thinks some experimental drugs now being developed by pharmaceutical companies might be better prospects. "We're mainly just reviewing our options now," he says. But if all goes well, he hopes to be able to begin a small clinical trial in as little as 6 months.

–Jean Marx