filter. "We hoped [finding the gene] would solve the slit structure," he says.

He and his colleagues screened the DNA of members of 29 Finnish families with the syndrome, including Toni's, for a genetic marker that is consistently inherited with the disease. By 1994, they had narrowed the gene's location to a portion of chromosome 19. Then Anne Olsen, an old friend of Tryggvason's, and her sequencing group at Lawrence Livermore National Laboratory in California chipped in and began sequencing the region thought to contain the gene. They turned up 11 candidate genes, nephrin's among them.

By last year, the researchers, including Marjo Kestilä in Tryggvason's group, had shown that the nephrin gene is mutated in affected members of their families and is therefore the one defective in congenital nephrotic syndrome. In more recent studies, Tryggvason's team, along with researchers at the universities of Helsinki and Oulu in Finland, confirmed that the protein is part of the slit diaphragm. As they reported in the July *Proceedings of the National Academy of Sciences*, they found that antibodies designed to home in on nephrin stick only to the diaphragm in the kidney glomeruli.

Because nephrin's structure resembles that of so-called cell adhesion molecules, Tryggvason theorizes that strands of the protein protruding from opposing foot processes form the interlocking teeth of the zipper seen by Harvard's Karnovsky a quarter-century ago. Some researchers remain skeptical of the proposed structure. For instance, nephrologist Larry Holzman of the University of Michigan Medical School calls it "reasonable speculation, but unproven."

Tryggvason says, however, that the model is bolstered by as yet unpublished studies in which Karolinska Institute structural biologist Ulf Skoglund used a novel form of electron microscopy to create three-dimensional pictures of the slit diaphragm. These show single nephrin molecules linking up just as Tryggvason suggested. But nephrin doesn't build the slit diaphragm alone, as Neng-Yao Shih, Shaw, and their St. Louis colleagues have now shown.

Last year, the Washington University team identified an intracellular molecule they called CD2AP (for CD2-associated protein) that apparently helps bring about the cell-to-cell interactions needed to activate the T cells of the immune system. But when the researchers knocked out the CD2AP gene in mice, they got a surprise: Although the resulting animals had weak immune systems, they died of kidney disease. Examining the animals' kidneys under the microscope, the researchers found that most of the mice's podocytes no longer bore foot processes, and their slit diaphragms were largely missing.

To find out whether CD2AP might work with nephrin to build the diaphragm, Shaw's team expressed the nephrin and CD2AP genes together in three different cell culture systems and found that the two proteins do in fact interact. The researchers suggest that CD2AP anchors nephrin to the internal protein fibers that form the podocyte cytoskeleton, thus helping form and stabilize the slit diaphragm. "This is a very important story," says Tryggvason. "It clearly tells you that CD2AP is important in maintaining the filter of the kidney and is probably important in connecting nephrin to the cytoskeleton."

Traditionally, kidney disease in adults has been blamed on external factors, such as certain drugs, or on damage caused by an unruly immune system. But the identification of the proteins making up the kidney's filter is awakening scientists to another possible source of adult kidney problems: mutations in genes encoding the filter proteins that weaken the kidney's structure. "It is very likely that mild mutations in nephrin, CD2AP, and other protein parts of the slit diaphragm might predispose people to [kidney disease]," Tryggvason says.

Currently, both his team and Shaw's in St. Louis are studying this possibility, although so far they have found nothing suspicious. If they do, they may provide a new handle on a whole range of devastating ailments, one that may someday help doctors successfully treat millions of suffering patients.

–INGRID WICKELGREN

INTERDISCIPLINARY RESEARCH

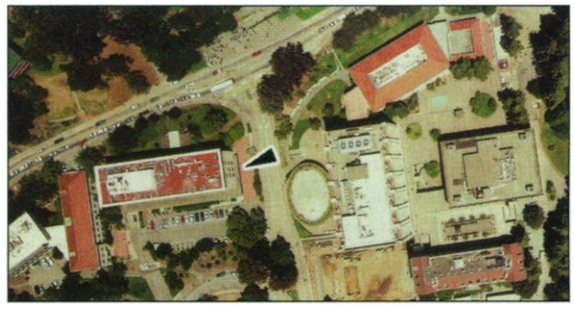
Berkeley Puts All Its Eggs in Two Baskets

To crack some tough research problems, Berkeley is bringing together fields ranging from physics to molecular biology in a new $500 million initiative

The first thing you notice when you take a seat on the couch in Adam Arkin's office at the University of California (UC), Berkeley, is a trio of wall charts staring you in the face. The first is filled with type so small that you have to stand up and peer at it closely to read the depressingly long lists of known diseases that may be lurking in your genes. The second and third charts detail genetic pathways involved in metabolism, in writing that almost requires a magnifying glass to read. But this bewildering array of genes, enzymes, and pathways is just the tip of the iceberg.

If the charts were to show all the connections and feedback loops among these metabolic players, "they would be completely black," says Arkin, a chemist and bioengineer with a joint appointment at UC Berkeley and the Lawrence Berkeley National Laboratory (LBNL). What is more, Arkin notes, the charts represent just a tiny fraction of all the genes, proteins, metabolites, and networks involved in running the human body. So, how can anyone make sense of genetic communications traffic that makes AT&T's telephone network look like a child's train set? "I don't know," says Arkin. "But that's what makes this such an interesting problem."

Meet the future of engineering. And mathematics, physics, and chemistry, for that matter. Oh, yes and, of course, biology. Also meet the future of UC Berkeley, now planning a major spending spree in support of interdisciplinary science to tackle such problems as Arkin's that span traditional scientific boundaries. As part of that endeavor, Berkeley officials announced this week that they have raised some $100 million in private funds toward the construction of two huge new research buildings in which researchers from departments ranging from physics and chemistry to molecular biology and public health will rub shoulders daily. When new money for programs and 15 new faculty positions are added to the mix, the total bill will likely approach $500 million, making it one of the most expensive interdisciplinary endeavors in the country, says Berkeley's Vice Chancellor Carol Christ.



Making way. Berkeley's Stanley Hall is set to be replaced by a new interdisciplinary research building.

CREDIT: A. VERA/UC BERKELEY

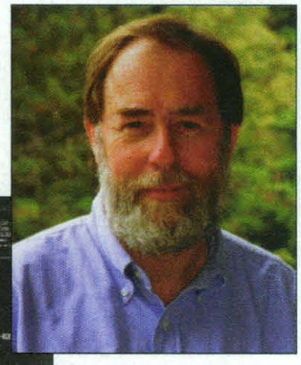
This focus on merging disciplines isn't new, of course. Labs with complementary goals have long found it easier to work together than go it alone. But in recent years, funding agencies such as the National Science Foundation have preached the gospel of integration, making money available for a network of interdisciplinary research centers. Now, universities have seen the light. Institutions as illustrious as Harvard, Stanford, and Princeton are among those attempting to break age-old departmental and disciplinary barriers to take advantage of new opportunities in genomics, biophysics, and nanotechnology. "Scientists today, for the most part, are much more entrepreneurial about using whatever technique works," says Ed Penhoet, who heads Berkeley's School of Public Health. "As a result, the old silos of biochemistry, molecular biology, and the like are really breaking down."

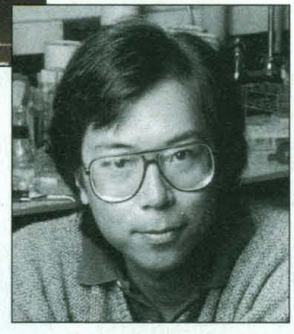
Among the new efforts pushing biology's integration with other fields, Berkeley's new project stands out as one of the boldest and most wide-ranging to date. The effort, formally known as the Health Sciences Initiative, will cut a wide swathe through the campus, involving some 400 scientists from at least 8 schools and departments. It will also bring in medical school researchers from across the bay at UC San Francisco, and physical scientists and engineers from LBNL. While most of the other new interdisciplinary efforts tend to focus on a particular area, such as Princeton's Institute for Genomic Analysis: "We're trying to do something a little bit broader," says Berkeley neuroscientist Corey Goodman.

Take Goodman's own field. Efforts to understand how molecular events give rise to human behavior requires coordinating the research of—among others—molecular biologists and geneticists who study the patterns of gene activation in neurons, cell biologists investigating synapses between neurons, researchers who study networks of nerves and patterns of neural firing, and psychologists studying behavior. "To understand the brain, you're not going to do it at any one level, which is the way it has been done up to now," says Goodman. "It's clear it will require an integration of these areas, but fueled by developments in the physical sciences," which are providing new tools, such as novel imaging techniques and ways to monitor gene expression.

The new initiative isn't the first time Berkeley has made a push for integration. In the 1980s, molecular biologist and former *Science* Editor-in-Chief Daniel E. Koshland Jr. spearheaded a move to collapse 12 separate biology departments—ranging from anatomy to biochemistry—into just two: integrative biology and molecular and cell biology. And last year the university launched a new neuroscience institute to bring together researchers from molecular biology and psychology to study the brain.

In each case, Berkeley researchers say two factors made the transitions possible. First was the creation of the Chancellor's Advisory Committee on Biology, an interdisciplinary group of faculty members who coordinated research, education, and hiring decisions in biology throughout the university. During the merger of biology departments, the committee proved vital for focusing on long-term research goals and fending off those intent on protecting the turf of their individual departments, says molecular biologist Robert Tjian, who currently heads the committee. And while the new interdisciplinary effort won't actually do away with any departments, "We're doing it all over again," says Tjian.





Coming together. Berkeley research leaders Graham Fleming *(top)*, Ed Penhoet *(left)*, and Robert Tjian are all pushing for integration.

The second key strategy was to sweeten the pot with some big investments, say Tjian and others. In both of the earlier efforts, Berkeley administrators included new research facilities in the package. That same carrot-minus-the-stick approach is being used again. At the east end of the Berkeley campus, Stanley Hall, a 4000-square-meter molecular biology building, is due to be replaced next year by a 15,200-square-meter "physical biosciences" building. That new behemoth will harbor researchers from molecular biology, chemistry, physics, and a new bioengineering department that was formally established this summer. Already, researchers in those departments are gearing up to work on data-intensive subjects, such as making sense out of the patterns of gene activation from DNA microarrays and surveying which genes are turned on in a given tissue. Meanwhile, administrators have similar plans to knock down the current public health building at the west end of campus and raise another 18,600 square meters of lab space devoted to neuroscience, cancer biology, immunology, and public health.

In both new buildings, researchers from the separate departments will share adjacent labs. "We certainly already collaborate with colleagues in other departments," says Berkeley physicist Dan Rokhsar. "But it takes planning. I spend a lot of my time walking to other parts of the campus. I need my next-door neighbors to be biologists to make the interactions more spontaneous," he says. Immunologist Jim Allison agrees: "If we're in the same place and the graduate students interact on a daily basis, I think good science will result from that."

So do researchers at other institutions, who see the Berkeley initiative as "far-sighted," as one researcher puts it. "I think it's amazing that they're spending that much money," says Scott Fraser, a molecular biologist who runs an interdisciplinary imaging research lab at the California Institute of Technology. Donald Tomalia, who helps run a new center at the University of Michigan that applies nanotechnology to biology, agrees. "Scientific questions don't care about disciplines," he says. "Efforts like this are important because it's critical to break down the barriers."

Still, the effort won't be all smooth sailing. One potentially divisive issue revolves around the teaching of graduate students. With the diverse mixture of disciplines, it is difficult to fathom how grad students can gain specialized knowledge in all their areas of research. With graduate programs already pushing many students beyond the customary 5 years for a doctorate, some worry that the need for additional specialized knowledge will require ever more course work. "We have big arguments in our department about extra courses," says Koshland. However, he adds, the solution can't be to pile on ever more classes. "The kids would never graduate if we made them learn everything," he says. "It's a core issue," agrees Goodman, and one that he calls "a work in progress."

Despite such challenges, many at Berkeley and elsewhere believe that if they don't embrace interdisciplinary work, research in their traditional departments will no longer remain competitive. Says Tjian: "The science is taking us in this direction." **–ROBERT F. SERVICE**

CREDITS: (CLOCKWISE FROM LEFT) CHIRON; G. BUTERA/UC BERKELEY; J. SCHERR/UC BERKELEY