GERMAN REUNIFICATION

Blending Biology, Technology, And Economic Development

JENA, GERMANY—For scientists, as for many others in Germany, reunification has not turned out to be quite the joyful coming together they had hoped for. Hundreds of laboratories and research institutes in the former East Germany were closed, making thousands of scientists jobless, while modernizing the remaining centers cost billions. Research in the west has also suffered painful cuts as part of the effort to bring money and jobs east.

Jena, a small eastern city with a century-old tradition in high technology, was hit hard when the two Germanys rejoined in 1990. One big blow was the drastic cuts at its dominant employer, a branch of the world-famous optics company Carl Zeiss, where 28,000 local people worked. And due to be shut down was the town's 1000-person research center, the Central Institute for Microbiology and Experimental Therapy (ZIMET). "[Jena] reminded me of Allentown, Pennsylvania, when the steel industry closed down," says American physicist Larry Brown, who recently moved to Jena from the Australian National University in Canberra.

But instead of dying, Jena is being reborn as a science city that combines strong technology with a new emphasis on life sciences. At the center of this renaissance is one of Europe's more unusual research centers, the Institute of Molecular Biotechnology (IMB). The 3-year-old IMB is already well on its way to becoming a major European center for engineering biomolecules and for the basic research behind this. It also has big ambitions to help develop a new generation of tools that will profoundly change biotechnology in the 21st century. "The IMB has the potential to become a leading center in the scientific community," says physicist Rudolf Rigler of Stockholm's Karolinska Institute. "If [mixing basic science and technology] can work anywhere [in Europe], it can work here."

The IMB's future is not yet completely assured, however. Faced with the heightened expectations of scientists and politicians at home, plus fierce worldwide competition in biotechnology, the IMB is still struggling onto its feet under the unique and difficult circumstances of reunification. This month marks an important milestone with the stepping down of its founding director, Austrian chemist Peter Schuster, who managed to establish world-class facilities amid considerable chaos. Whether the institute fulfills its early promise will depend largely on who its board of trustees names next week as the new director, to take over at the end of this year.

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Biological spark plug. The Institute of Molecular Biotechnology is at the center of a high-tech strategy to revitalize the city of Jena.

Teamwork. One of the keys to Schuster's success at IMB has been gathering together scientists of many stripes to create a blend of cutting-edge biology and state-of-the-art technology—a rare combination in Europe. The IMB's 14 research groups include basic biologists, mathematicians, physicists, and engineers. IMB researchers also mine rich resources in the vicinity, such as the expertise in materials science and nanoscale engineering at the neighboring Institute of Physical High Technology (IPHT).

With this blend of skills, IMB is becoming one of Europe's major players in a fast-growing new field that is exciting scientists worldwide: evolutionary biotechnology. The name refers to a set of strategies that allow researchers "to evolve molecules in the test tube to meet their own needs ... in a period of a few weeks," says Larry Loeb of the University of Washington, Seattle. The idea is to "start with a natural product and then adapt it to special purposes the way nature does: by Darwinian selection," explains Manfred Eigen, a Nobel Prize–winning physicist at Göttingen's Max Planck Institute for Biophysical Chemistry. Eigen is one of the field's pioneers and was a driving force behind the IMB's creation.

Stepping down. Peter Schuster steered IMB through its first 3 years.

First, researchers generate variants in the molecule of interest, either by copying its gene in an error-prone system or by incorporating stretches of random sequences using a powerful new technique called "combinatorial chemistry" that can produce millions of different molecules and keep track of their precise structures (*Science*, 3 June 1994, p. 1399). Then they select or screen for molecules with a desired trait—say, a faster acting enzyme or a tighter binding inhibitor. "It's an enormously powerful way of creating new molecules," says Loeb.

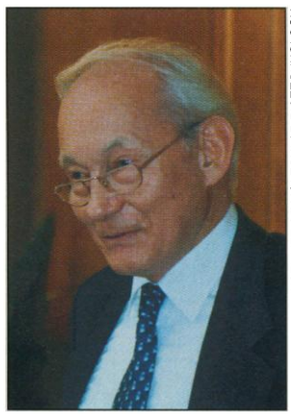
One of the trickiest parts of these evolutionary strategies is handling the millions of samples involved. The IMB is focusing its interdisciplinary skills on automating this task. Along with IPHT scientists, Schuster's group has begun work on an integrated system for synthesizing and screening molecules using 20-centimeter silicon wafers with up to a million microscopic reaction chambers on their surfaces. Liquid jet pipettes inject minute doses of reactants into the chambers, and optical systems detect the molecules. To fish out the rare, sought-after products, the system will incorporate an ultra-sensitive, fluorescence-based scheme developed by Eigen and Rigler (*Science*, 1 July 1994, p. 32). Now capable of detecting and trapping one molecule in 10^{15}, further work at the IMB should increase this to one in 10^{18}, according to Eigen. "It's a truly amazing machine," says Loeb.

The development of such nanotechnologies for biological research is "a revolution in the making," says University of Heidelberg physical chemist Jürgen Wolfrum. He predicts it will change biology profoundly—permitting unprecedented manipulations on single cells and even individual molecules—just as the microscope did by revealing nature at the micrometer level. And Jena's scientists, he says, are just the right interdisciplinary mix to be at the forefront.

Inauspicious beginnings. Few would have guessed, 4 years ago, that Jena would now be housing such a thriving research center. Indeed, all the east's nonuniversity research institutes were due to close at the

end of 1991 under the reunification agreement. But the group of mostly West German scientists who reviewed ZIMET in spring 1991 saw Jena's huge potential in technology and, rather than letting it wither, they recommended building up a life sciences campus strong in biotechnology. ZIMET was carved into three university departments and two independent centers, one of which became the IMB.

When the IMB opened in January 1992, Schuster faced a daunting task. The confusion surrounding ZIMET's closure the week before left the 150 scientists, technicians, and support staff retained by IMB unsure who they worked for, what to do, or even whether they would have jobs for much longer. The labs had not been modernized since the 1950s and were unfit for much of the planned research; telephones barely worked, and computer networks were nonexistent.



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Driving force. Manfred Eigen helped IMB get started.

But these difficulties seemed to bring out the best in people. "I've never worked on anything in Germany where the atmosphere was so positive," says Hermann Bujard, director of Heidelberg's Center for Molecular Biology and a member of IMB's founding committee. "In [western Germany] we're used to hearing, 'No, that can't be done.' [In Jena], despite the chaos, people did everything possible to get the job done." The IMB also had strong support from politicians eager to revive the city, and lots of government money. And there was Schuster—whose tact, patience, and "Viennese charm" were crucial to making it all work, says Bujard.

Schuster also succeeded in recruiting an interdisciplinary, international team. Brown was drawn by the institute's "very farsighted vision" and the chance "to be around a very complementary group of people." Physicist Stephan Diekmann was looking for a more open atmosphere than he had found in West Germany. "It's a particular type of person coming here," he says, "people who want to shape their environment. I knew it would be chaotic. ... But I meet more free spirits here."

Diekmann was also attracted by the chance to apply IMB's expertise to his own pet project: using purified enzymes to remove nitrate contaminants from drinking water. Nitrates are a widespread problem due to heavy use of chemical fertilizers, which eventually seep into ground water, and there are no good methods to get rid of them. Diekmann's solution is a "bioreactor"—a cheap, efficient apparatus containing three immobilized enzymes that reduce nitrates to harmless nitrogen gas. The natural enzymes work reasonably well in laboratory prototypes built by Diekmann's Göttingen-based company, Mobitec. But he and co-worker Peter Steinrücke want to improve them.

At IMB, Diekmann can count on lots of help. Rolf Hilgenfeld will try to crystallize the enzymes, and Brown will analyze them by nuclear magnetic resonance. With this information the researchers can then turn to IMB's computer modelers and evolutionists for advice on how to make the enzymes smaller, for example, or longer-lived, or able to work without cofactors.

It is projects like these, with real industrial applications, that help make IMB a key part of the "Jena model" for boosting the region's technology—a plan being watched closely all around Germany. Signs are that it is working: Helped by strong financial incentives from government and cheap, plentiful lab space, 140 technology-based companies have started up in Jena since reunification, according to its Chamber of Industry and Commerce. And the number should grow as regional planners amass a larger fund to help tiny companies onto their feet in a country where venture capital is almost nonexistent. Says Stefan Seeger of the University of Heidelberg, who moved his small laser company, SL Microtest, to Jena: "I like the dynamic feeling ... the incredible pool of talented technical people [and] ... a level of support which doesn't exist in [western Germany]. Jena will be *the* place for technology in Germany."

And it is not just Jena that could benefit. Some researchers are hoping IMB can kickstart Germany's dormant biotechnology industry. The country was left behind in this fast-moving area due to its highly bureaucratic safety regulations and hostile public opinion (*Science*, 31 January 1992, p. 524). But it will be tough going: There are already dozens of labs and companies in the United States pursuing evolutionary strategies, says Gerald Joyce of the Scripps Institute in La Jolla, California, who runs one of the major labs in the field.

Growing pains. While the IMB works hard to catch up, it still faces uncertainties. The most important is the change of leadership. Physical chemist Günter Maass of Hannover's Medical University becomes acting director next month when Schuster steps down. Maass, in turn, will hand over the reins at the end of 1995 to the director who will be named next week. The transition should be eased, however, by the fact that Schuster will keep a group at the IMB, along with a part-time affiliation.

At the same time, the institute is still struggling to refit its old buildings: Only a third of the labs are fully functional, another third have only just been finished, and the remainder will take at least another year. This means more researchers moving to temporary labs and "fitting experiments to circumstances," says Brown. Besides delaying research, the moves also severely limit interaction between groups, says physicist Günter Löber—a problem for the multidisciplinary approach being pursued at IMB. "For the advantages of this place to be realized, communication has to be better," he says—a sentiment echoed by most of his colleagues who spoke with *Science*.

And despite the progress so far, problems of reunification still haunt the institute. To many easterners, reunification was more like a West German takeover that left them second-class citizens in their own country. For scientists, these feelings were fueled by the west's decision to close eastern research laboratories and institutes en masse, with only a hand-picked minority of easterners holding onto jobs and many newly vacant posts—especially those at the top—going to West Germans.

Although IMB's problems are mild compared to those at many other eastern labs, "east-west issues are on the agenda every day," says one newly arrived western scientist. Easterners make up 50% of the staff, but most hold technicians' posts, and only one of the eight most senior researchers is from the east. That creates a "very unequal situation," says eastern biochemist Bernhard Schlott, as senior people usually have more institutional money to pay group members and therefore a "more solid, completely different basis for their work." The disparities are reinforced by federal rules that give most westerners working in the east 20% more pay than their eastern colleagues.

And a recent change to IMB's still-provisional bylaws seems to have made matters even worse: By restricting voting rights among group leaders to the most senior ones, easterners are almost completely cut out. The issue is purely symbolic, admits Löber, because internal votes are not binding on the director. Nevertheless, he says, the change was "a blow to our dignity."

But despite the problems, Löber says, "easterners at the [IMB] are well integrated. ... We are not just followers. ... We owe that largely to Schuster. It really paid off that the director was not a West German. It took the edge off a difficult situation." As Schuster steps down as director, IMB's researchers are hoping that his successor will be as skillful. Says Diekmann wistfully: "I look forward to the days when the [IMB] no longer has extra reasons to have problems ... but has only normal problems."

–Patricia Kahn