MOLECULAR BIOLOGY

Chambon Builds Institute With U.S. Funds and Eye for Detail

ILLKIRCH, FRANCE—Molecular biologist Pierre Chambon is a stickler for detail. Last year, when his research team of 300 scientists moved from its cramped quarters in the center of Strasbourg to a spacious new building in this suburb just outside the city, Chambon took charge of nearly every aspect of the move. "Pierre wouldn't let the bulletin boards be installed on the walls until he had checked that they were aesthetically correct," says one researcher, who prefers to remain anonymous. Yet for scientists at the new Institute of Genetics and Molecular and Cellular Biology (IGBMC), Chambon's involvement in such minutiae allowed research to continue almost uninterrupted. "The move was fantastically well organized," says cancer researcher Paul Basset. "We only lost 1 or 2 days of lab work."

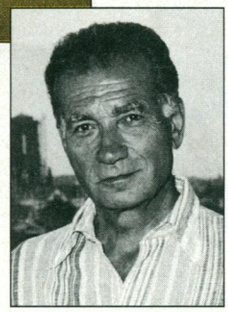
But moving 300 scientists 5 kilometers down the road was small potatoes compared to Chambon's most stunning accomplishment at Illkirch: building a major new research institute at a time when French science is suffering from cutbacks and budget freezes (*Science*, 7 July, p. 22). To pull off this feat, Chambon needed a whopping dose of outside help. He got most of it from the U.S.-based pharmaceuticals giant Bristol-Myers Squibb (BMS), which picked up 90% of the new building's $40 million construction costs, with the French Association for Cancer Research stumping up the remaining 10%. Chambon's normal funders—public agencies including the Centre National de la Recherche Scientifique (CNRS), the biomedical research agency INSERM, and Strasbourg's Louis Pasteur University—pitched in with $20 million for equipment, and BMS has also agreed to contribute an initial $4 million per year to support the institute's ongoing research.

In return for its generosity, BMS has been granted exclusive patent rights on certain IGBMC projects. But while BMS executives hope that their investment will eventually pay off, one thing they do not get for their money is the company name on the building. This honor is reserved for CNRS, INSERM, and Louis Pasteur University, which pay the salaries of staff scientists—making the IGBMC the first public research institute in France to be constructed by private industry.

It should be no surprise that BMS chose to entrust so much of its money to Chambon. His research group ranks sixth in the world among institutions of molecular biology and genetics (by citations per published paper), and number one outside the United States, according to the Institute for Scientific Information. This puts the IGBMC well ahead of other European powerhouses such as the U.K. Medical Research Council's Laboratory of Molecular Biology in Cambridge and the European Molecular Biology Laboratory in Heidelberg, Germany.

The deal with BMS shows that Chambon, one of France's most powerful and charismatic researchers, is still doing things his own way. "He's intelligent, aggressive, and he works very hard," says immunologist Diane Mathis, a co-leader of one of the IGBMC's 30-odd research groups. And Denis Duboule, a developmental biologist at the University of Geneva who spent several years in Chambon's lab during the 1980s, says that Chambon "can somehow anticipate what is going to be the important [research] in the future. And from the time he's anticipating, he's acting—this is the big difference."

PHOTOS BY JEAN-MARC LAFONTAINE



Smart move. Pierre Chambon *(right)* and his new institute, built with industry money.

Indeed, Chambon's willingness to leap into new areas of research is a major key to his success. A pioneer in the study of gene expression in the 1960s and '70s, Chambon has since turned his attention to cancer research and developmental biology. Yet he has always kept plenty of troops stationed on the projects he himself has left behind (see box). And despite the tremendous growth of his army of scientists over the years, he continues to guide his research empire with a firm hand. For example, although each of the IGBMC's research groups is scientifically independent, Chambon insists that all grant money brought to the institute be put into one large pot—and he alone makes the final decisions about how funds are distributed.

"Pierre is a benign dictator," says *Drosophila* geneticist Pat Simpson, who has worked under the Chambon umbrella for almost 15 years. "But he has never interfered scientifically. I've had complete freedom to do what I wanted." Moreover, says Simpson, "Pierre lets relatively young people become group leaders, and that's not a general situation in France." Chambon says that helping younger scientists is one of the primary reasons for the funding-pool policy. "The lab should not be a jungle," he says. "Everyone in this lab has the right to work and should have access to what is required." And he readily admits that he makes the ultimate decisions about how the institute is run. "I don't put 10 people around a table to discuss everything," Chambon says, "because this is useless and takes a lot of time. But I talk to several of the group leaders and ask them what they think."

Nevertheless, some researchers at the IGBMC say privately that Chambon's authoritarian leadership sometimes goes too far. In one celebrated episode, a group leader complained about one of Chambon's economy measures, which allows each scientist only one box of latex gloves each month. When the researcher explained that his lab had recently begun working with radioactive reagents and that one box was not sufficient, Chambon gave the matter some thought. "Okay," Chambon said at last, "you can have one and a half boxes."

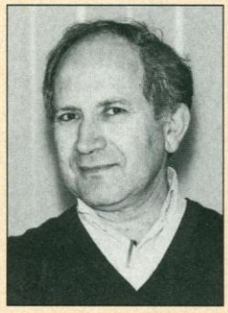
Chambon's insistence on having his way paid off in his negotiations with BMS. When company executives began thinking about building a major in-house research facility in France several years ago, they asked Chambon to be its director. "I said no," Chambon recalls, "because I've been in public research all my life, and I'm sentimentally attached to this lab." Instead, Chambon convinced the company to build him a new public institute as well as provide direct support for research. In return, BMS retains a proprietary interest in three research areas that might lead to therapeutic products: the role of retinoic acid and its derivatives in mammals, immunological work on diabetes and arthritis, and the possible role that certain enzymes may play in the spread of breast cancer.

Before signing the contract with BMS, Chambon says he talked it over with Hubert Curien, who was France's research minister at the time. "I said, this is the American offer; please ask French industry if they are inter-

Riding the Waves of Molecular Biology

Like a surfer for whom catching a wave has become second nature, Pierre Chambon has been riding the big waves of molecular biology for more than 30 years. He helped unveil some of the central mysteries of gene expression, including the key discovery in 1977 by his and other groups in Europe and the United States that the sections of genes that code for amino acids in higher organisms can be split into several separate segments.

In more recent years, Chambon has turned his attention to human genetics, cancer research, developmental biology, immunology, and structural biology. But as his team has expanded from a handful of students back in the 1960s to its current incarnation as the sprawling Institute of Genetics and Molecular and Cellular Biology (IGBMC), Chambon has mastered the art of keeping lots of torches lit at the same time.



Egly. Carrying the gene-expression torch.

The secret of Chambon's success, says longtime associate Jean-Marc Egly, is that "he is still a kid; he still loves to do science." Egly is one of several IGBMC researchers who continue to study gene expression, focusing on a group of proteins, called general transcription factors, which bind to DNA and turn on the cell's protein production machinery. Recently, Egly's lab has discovered that one of these transcription factors—known as TFIIH—is implicated not only in regulating gene expression but also in the repair of damaged DNA and control of the cell cycle, indicating a direct relationship between these three cellular processes. This could lead to a better understanding of certain genetic diseases previously linked to DNA repair malfunctions, including xeroderma pigmentosum and Cockayne's syndrome.

The pharmaceuticals giant Bristol-Myers Squibb, which footed most of the bill for the IGBMC's construction, has taken a keen interest in the work of its breast cancer unit. For the past several years its leaders, Paul Basset and Marie-Christine Rio, have studied a family of enzymes known as matrix metalloproteinases, which appear to break down the large organic molecules that help hold cells together. Normally, these enzymes play an important role in an organism's development, but their production at the wrong time and place can lead to trouble. For example, the enzyme stromelysin-3 (ST3) is produced in significant quantities by many cancer cells and is thought to be involved in metastasis, the process by which cancer cells break out of a tumor and spread to other parts of the body. Basset, Patrick Anglard, and others at IGBMC and Paris's Institut Curie recently isolated the human ST3 gene and characterized the promoter region which controls its transcription. This could lead to therapies targeting cancer metastasis.

And with the opening of the IGBMC, Chambon has brought in a whole new flock of young developmental biologists. Among them are Christine Thisse, Bernard Thisse, and Uwe Strahle, who will probe early genetic and molecular events in the zebrafish, a species whose transparent embryos make it ideal for studying the development of vertebrates (*Science*, 13 May 1994, p. 904). Other recent recruits include Michel Labouesse, who joined Chambon 3 years ago and has already made great strides in unraveling cell fate in the nematode worm *Caenorhabditis elegans*.

IGBMC researchers, including Chambon himself, are also looking at the development role played by the vitamin A derivative retinoic acid, a dietary component necessary for normal growth, vision, reproduction, and other key physiological processes. Many researchers suspect that retinoic acid can act as a morphogen, influencing the fate of cells according to their position in the embryo. A team led by Chambon, Manuel Mark, and Philippe Kastner has been using gene-targeting techniques in mice to "knock out" the genes for certain retinoic acid receptors. In most cases, knocking out one receptor gene had little or no effect, but double knockouts of two receptor genes often led to severe developmental abnormalities. And, in a particularly dramatic result, some of these double mutants developed skulls with atavistic elements typical of reptiles—leading Chambon to speculate that during the evolution of mammals, retinoic acid may have helped to modify reptilian features.

Throughout the ups and downs of French research funding, Chambon has managed to recruit—and hold together—one of the world's most high-powered research teams. "I would be very astonished if anyone would leave, at least for another [lab] in France," says human geneticist Jean-Louis Mandel, a Chambon associate since 1967. "There's no place they would have better conditions."

–M.B.

ested," Chambon recalls. "I didn't want people saying afterward that I had sold French science to the Americans. So [Curien] did that, and they all said it's a fantastic idea, but we don't have the money."

Leon Rosenberg, president of BMS's Pharmaceutical Research Institute, says his company's willingness to pick up the tab for the new institute was motivated by business, not altruism. "Senior management believes this has to be an investment and not a grants program," Rosenberg says, adding that the company's internal R&D efforts must be complemented "by mechanisms for capturing valuable information from the outside."

And although Chambon's agreement with BMS will allow the IGBMC to continue its emphasis on basic research, he admits that the inflow of industry money—particularly at a time when public funding for research is dwindling—has the potential to influence his team's scientific direction. "There's a danger that people will not attack some problems because they cannot get support," he says. "If I have a choice of enlarging our *Drosophila* group or starting a group on hematopoietic [blood-cell precursor] cells, I will probably give priority to hematopoietic cells, because I know there's the possibility of getting money from industry."

So far, at least, BMS seems content to sit on the sidelines and benefit from whatever the IGBMC comes up with. But Rosenberg warns scientists against expecting companies to plug the gaps in public science spending. "I see no likelihood that industry will be able to substitute for government in the support of academic research," he says. And Chambon agrees that, at least in France—where industry is either unwilling or unable to give large sums to basic research—the IGBMC "cannot be a model for the future. ... The circumstances were rather exceptional."

Thus for Chambon, who says that at the age of 64 he has begun thinking about retirement, the IGBMC may well end up being a lasting legacy to French science. Indeed, the contract with BMS stipulates that after 50 years the building will be deeded over to France's public research agencies. As for how the institute's 300 scientists will carry on once their leader is gone, Chambon says he is not worried. "They are all strong characters," Chambon says. "But even if they don't realize it, they were chosen for their ability to work together."

–Michael Balter