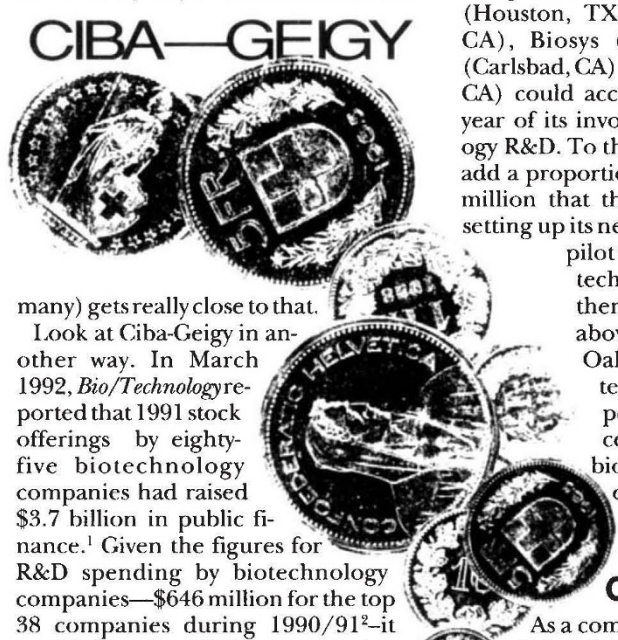
BY JOHN HODGSON

The First of the Big Spenders

There are a number of myths about biotechnology that *Bio/Technology*, as its ears and voice, ought to correct. One of them, put about by some CEOs trying to grow small companies, is that there are only two countries in the world that are really active in biotechnology: the United States and the United Kingdom. If you are trying to raise speculative capital to fund your growing business, or if you gather your information on biotechnology from the general media (which tends to get information from those trying to raise speculative capital), then you might be forgiven for reaching that conclusion: with a few exceptions, notably Australia and The Netherlands, venture and subsequent phase money for biotechnology is a scarce commodity away from the Northern Anglo-Saxon axis. However, if you look beyond the bubble and fizz of fund-raising, behind the froth and pop of public relations, to the strategy and toil of making money by producing and selling products in biotechnology, that conclusion is palpably untrue.

One sure way of getting a truer perspective on biotechnology is to go into a major chemical company involved in pharmaceuticals, agrochemicals, and seeds. And, if you have to choose one company, there is a good reason for making it Ciba-Geigy of Basel in Switzerland: Ciba-Geigy is the company that has the most to gain (or to lose) from biotechnology in the next decade. That is to say, compared with pharmaceutical specialists like Merck (Rahway, NJ) or Glaxo (London), or with chemical concerns such as ICI (London), DuPont (Wilmington, DE) or Hoechst (Frankfurt, Germany), more of its turnover is in areas that will certainly be impacted by biotechnology [See Tables 1 and 2; data from *Scrip* and from County NatWest WoodMac (Edinburgh, U.K.)]. In its 1991 results, announced in March 1992, 60 percent of Ciba-Geigy's turnover—SFr.12,622 million ($8,500 million)–was either in health-care or in agrochemicals/seeds. Only Bayer (Lever-kusen, Germany) gets really close to that.

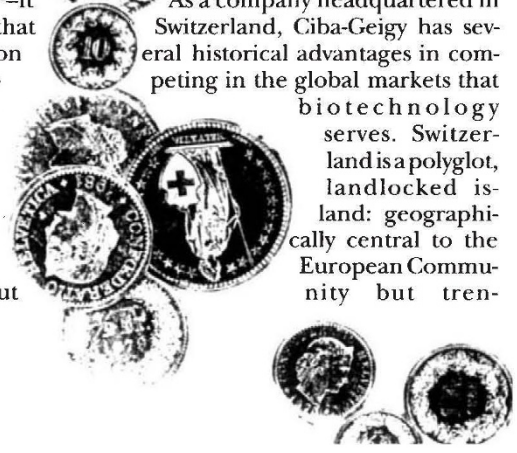


Look at Ciba-Geigy in another way. In March 1992, *Bio/Technology* reported that 1991 stock offerings by eighty-five biotechnology companies had raised $3.7 billion in public finance.[1] Given the figures for R&D spending by biotechnology companies—$646 million for the top 38 companies during 1990/91[2]–it wouldn't be unrealistic to assume that most of that money will be spent on research and product development over, say, the next 2-3 years. Now compare Ciba-Geigy. For 1991, it increased its group R&D spending 7 percent to $1.5 billion; that is, in one year, one company put into its R&D 40 percent of the money that the entire investment community put into biotechnology in its most generous spree ever. Of Ciba's $1.5 million, around $100 million was devoted to biotechnology activities, with around $65 million for biopharm-aceutical development.

In addition, Ciba-Geigy's recent investments and collaborations with U.S. companies such as Tanox Biosystems (Houston, TX), Chiron (Emeryville, CA), Biosys (Palo Alto, CA), Isis (Carlsbad, CA) and Affymax (Palo Alto, CA) could account for $20 million a year of its involvement in biotechnology R&D. To that one should certainly add a proportion of the estimated $80 million that the company will spend setting up its new Biotechnikum R&D/pilot facility in France. In biotechnology R&D spending, therefore, Ciba-Geigy is way above Amgen (Thousand Oaks, CA) and exceeds the ten most profligate European biotechnology concerns put together[3]: of the biotechnology specialists, only Genentech (South San Francisco, CA) spends more.

Claustrophobia

As a company headquartered in Switzerland, Ciba-Geigy has several historical advantages in competing in the global markets that biotechnology serves. Switzerland is a polyglot, landlocked island: geographically central to the European Community but tren-



chantly resistant to becoming part of it legally or politically. It is a small country. Its six and half million people have provided neither a sufficiently large home market nor an indigenous skills base to satisfy either the drive of the country's major manufacturers for expansion or the ambitions for high standards of living of the six and a half million people. For Swiss companies, the dissolution of national barriers in Europe that 1993 is supposed to bring will bring no change of strategy—they have always yearned for outside markets and have traded globally.

Being in Switzerland seems, at present at least, to have disadvantages, too. A strident minority of those six and half million people, vociferously trammeling all available avenues in the highly participatory Swiss democratic system (see *Dateline*, this issue), has proved to be a thorn in Ciba-Geigy's flesh. Ciba submitted its plans for a new R&D/pilot laboratory, the Biotechnikum, to the Basel authorities in 1990, expecting that the facility would come on stream in 1992. The plans were approved—but only in July of 1991. In the face of those delays, and anticipating more, Ciba withdrew its Basel applications in December 1991 and applied instead to the French authorities to build the Biotechnikum at another company site across the River Rhine. The company now expects to complete construction at Huningue, Alsace 4-5 years from now. Kaspar von Meyenburg, Ciba's head of biotechnology, was disturbed by the delays in approval: "It was an unhealthy surprise to have it take so long in this town of Basel [where the chemical industry is such a major employer]; so now we are going to move to France."

In May, Ciba had another "unhealthy surprise" brought about by its sensitivity to public uncertainty about biotechnology—this time with respect to its plant breeding activities. The company had planned to conduct a small-scale field trial of a recombinant commercial maize variety containing a marker gene. The variety used and the scale of the test were similar to experiments approved and completed last year by the company in France and the U.S. However, because there is no designated approval authority in Switzerland equivalent to the French Commission Genie Biomoleculaire (CGB; Paris) or the USDA's Animal & Plant Health Inspection Service (APHIS; Washington, DC), the trial will not go ahead—even though a Swiss committee of experts had concluded that the test presented no risk to either man or environment. "It was our decision, based on the company's ethical policy," said Ciba spokeswoman, Elke Jarchow. Perhaps Ciba's discretion will prove the better part of valour. But from outside it looks like a cave-in in the face of lethargic bureaucracy and aggressive activism.

Table 1. Top 10 pharmaceutical companies worldwide 1990-91.

Company	Pharm. Sales	% change vs 1989/90
Merck & Co.	6365	+17.8
Glaxo	6062	+16.3
Bristol-Myers Squibb	5261	+18.4
Hoechst	4992	+18.8
Bayer	4956	+16.9
Ciba-Geigy	4582	+21.3
Eastman Kodak	4349	+8.5
SKB	4242	+15.6
Sandoz	4088	+18.0
Eli Lilly	3700	+26.1

Source: *Scrip* pharmaceutical company league tables.

A PILLAR OF DRUG DISCOVERY

Despite being sixth in the pharmaceutical sales league [Sfr.7,824 million ($5,350 million); Table 1], only Voltaren, Ciba's non-steroid anti-inflammatory drug for arthritis tops $500 million a year in sales (and those sales might be affected as Ciba begins to take on board severe criticism from FDA (Bethesda, MD) of its Voltaren promotion in the U.S.). The company seems to maintain its strengths in inflammation, cardiovascular disease, and hypertension by gradual improvement and force of numbers rather than dependence on a few blockbusting drugs: for instance, its hypertension drug, Lotensin, received only a 1C rating (new chemical entity with little or no significant improvement over existing therapies) when approved recently by FDA. One pharmaceutical industry observer summarises Ciba's position as being "in some very big indication areas but often with unexciting products."

Biotechnology and the 250-strong pharmaceutical unit at Ciba in particular might just change all that, according to Kaspar von Meyenburg. "I believe that going into new areas, looking at new molecular targets, will bring beneficial effects in new areas leading to novel mechanisms and novel compounds. Some of those activities [but not all] will be within our existing areas of strength." Yet von Meyenburg is keen to stress that biopharmaceuticals and biotechnology in general are but a small part of Ciba's R&D approach: "We use biotechnology as a set of tools to produce novel substances that one had no way previously of producing or finding. These substances will not replace existing drugs or effective new drugs." Von Meyenburg sees biotechnology as something that "complements the conventional approaches," as "a modern pillar of drug discovery."

Lack of production capacity may, in one way at least, have constrained Ciba's efforts in biopharmaceutical development. According to von Meyenburg, Ciba has "always been limited [in bio-logicals production] during the past five years. We have a somewhat elderly facility— cranking out all sorts of wonderful compounds—and we will be even more limited in the future as clinical demands increase. We endeavour, therefore, to have close collaborations with outside companies; Synergen, Chiron, Tanox, for instance—that's one way of having more facilities."

BETTER THAN CURE

Ciba has made use of Chiron's yeast production facility in Emeryville to produce what are probably the nearest-market of its recombinant products. In 1987, Ciba established The Biocine Company as a 50/50 joint venture in vaccine development with Chiron. A year later, the Swiss major took a $20 million equity stake in Chiron. Now Biocine has four vaccine candidates in phase-II clinical trials: an influenza vac-

cine, a modified gp-20 AIDS vaccine, a glycoprotein subunit vaccine against genital herpes that may have potential as a therapeutic, and a malaria vaccine based on *P. vivax* circumsporozoite surface antigen. In addition, the joint venture is developing candidate vaccines for hepatitis C (phase I). Chiron's earlier-stage viral vaccines—for hepatitis A and cytomegalovirus, for instance—might also enter the Biocine development pipeline.

Nearest of all its recombinant vaccines to the market is a whooping cough (pertussis) vaccine that came to Ciba when Biocine acquired Sclavo (Siena, Italy). The vaccine is a toxoid from *Bacillus pertussis* that has been detoxified by substituting for lysine and glycine residues in the S1 subunit. The product is expected to reach the U.S. market in 1993. The Sclavo acquisition also brings Biocine an existing conventional vaccine business that had sales in 1991 of Llt. 55 billion ($45 million).

Ciba appears to be looking to maximize its benefits from the vaccine products that are now appearing on the horizon. As a result of a deal struck in January 1992, Ciba may reap the lion's share of Biocine's earnings: over the next four years it will invest $45 million in the joint venture above its existing contributions in exchange for "a preferred interest" in the earnings. Chiron can maintain its 50 percent stake in Biocine by repurchasing 50 percent of Ciba's preferred position before March 31st 1996 for an amount equal to Ciba's preferred investment plus interest.

Immunologicality

Ciba's involvement in vaccines development is relatively recent and stems primarily from its continuing work in immunology: its immunostimulatory compounds, such as muramyl tripeptide (NTP-PE/MF-59), are used as adjuvants in several of the Biocine vaccine candidates. The thread of immunology runs through other of Ciba's development work including two of the more advanced biopharmaceutical developments. First, there is the anti-IgE antibody produced by Tanox and licensed to Ciba that is about to enter clinical trials as a treatment for allergy (Ciba also has its own anti-IgE at an earlier stage of development). And then there is Ciba's recombinant thrombolytic hirudin, which, like other leech-derived compounds is remarkable for its non-immunogencity. Hirudin entered phase II trials in Japan in September 1991 and demonstrated coagulant properties at doses of 0.02- 1.0 mg/kg.

Behind this advanced guard comes a slew of early-stage projects. Extending its work on leech products, Ciba has cloned the gene for the protease inhibitor Eglin C, and is looking at using the protein as a possible therapeutic in protease-associated conditions such as emphysema, septic shock, arthritis, and osteoarthritis. In October 1991, Ciba entered a collaboration with Isis Pharmaceuticals to develop an antisense approach to inhibiting the expression of the endothelial cell adhesion molecules ICAM and ELAM. Another immunological project is the development of its own anti-IgE monoclonal antibody in allergy.

Table 2. Top ten agrochemical companies by turnover: Estimates for 1991.

Company	Rank	Sales Range ($M)
Ciba-Geigy	1	>3200
Bayer	2	
ICI	3	2100-2300
Rhone-Poulenc	4	
Du Pont	5	
DowElanco	6	1500-1800
Monsanto	7	
Hoechst	8	
BASF	9	1000-1500
Schering Plough	1	

Source: Data from County NatWest WoodMac (Edinburgh, U.K.).

Clinicality

Ciba is also involved with clinical studies on a number of other recombinant products outside immunology: *insulin-like growth factor-1 (IGF-1)* produced in yeast by Chiron (Ciba is the worldwide licensee) has been in phase II trials for type II diabetes and acute renal failure; an *anti-HIV monoclonal antibody, BAT-123*, isolated by Tanox (another company in which Ciba has a minority equity stake) has undergone phase I trials in Switzerland and has been well-tolerated; and patented *hybrid lymphoblastoid-derived interferons* are in late phase I against cancer and viral disease.

Ciba is also going beyond the isolation and production of biological products to screening for active small molecules. However, this is an area about which Kaspar von Meyenburg is somewhat cagey: "If you [as a company] are in blood pressure, and we have blood pressure control drugs, then it would be an obvious conclusion that we are probably using high-technology screening in this area: angiotensin II and its receptor, renin, would be obvious targets. The same logic would apply in inflammation, for instance with interleukins, or in allergy with IgE." Additional work with high technology screens takes place in the separate therapeutic units at Basel.

As in other areas, Ciba supplements its in-house efforts with outside collaborations. In July 1991, the company established an agreement with Affymax covering product discovery research directed at selected molecular targets in arthritis, cancer, and autoimmunity. As with its collaborations with Chiron and Tanox, Ciba has taken a minority equity stake in Affymax, 5-6 percent in this case. While taking responsibility for clinical development and gaining exclusive worldwide marketing rights to any products developed, the pharmaceutical company will provide Affymax with R&D funding, milestone payments, and royalties on sales.

Tanox, Affymax, Chiron, Isis, Genentech: Ciba is collaborating with them all. It has also broken off its two relationships with Synergen (Boulder, CO), one through its Zyma subsidiary for recombinant fibroblast growth factor. Kaspar von Meyenburg is quite clear on the difference between these biotechnology companies and companies like Ciba. "Their business is developing technology.... Our projects are in the direction of treatment."

Agrophilia

In healthcare, Ciba maintains a deliberate policy of enhancing R&D through alliances. In the agricultural sector, however, the nature of those alliances has

changed with time. "There has certainly been an evolution in our external collaborations," explains John Duesing, Head of Research Services at Ciba-Geigy Seeds: "In the early days, we were not sure where the underlying principles were going to lead so we put a lot of seed money into general biology. Now we have either brought the technology in house, identified collaborators, or moved away from specific areas. We are not as diversified as we were."

That focussing-in can be seen in the way Ciba has gathered biological technology around its maize and wheat breeding programme. It was the first company to regenerate fertile maize plants from protoplasts, and in 1991 conducted field trials on recombinant maize in both the U.S. and France. It licensed in "biolistic" technology from DuPont, and has used it sucessfully with maize. The company was granted a U.S. patent covering the genetic sequence of the maize nitrate reductase and has recent application for a European patent on root-specific promotor sequences.

Maize on the map

Perhaps one of the most important technologies that Ciba-Geigy Seeds has taken in-house and refined is RFLP gene mapping in maize and wheat. The technology was licensed on a non-exclusive basis from the Agricultural Genetics Company (AGC, Cambridge, U.K.), another company in which Ciba has an equity stake (5.1 percent). Other licensees include ICI, Nickerson International Seed (Cambridge, U.K.) which is now part of Limagrain (Gerzat, France), and Unilever's Plant Breeding International (Cambridge, U.K.).

Ciba project manager Philippe Gay contrasts the aims mapping in plants with that for the human genome: "In human genetics, the goal is to walk to the gene. In plant breeding, there is no need ... all you need is a decent linkage to the gene of interest." The company's knowledge of the genetic map in wheat and maize has already been implemented in its breeding programmes, according to Gay. But as important, he says, is that Ciba can look beyond single gene traits: "We are now handling projects involving more complex traits where there may be five separate loci involved. ... What we are trying to do is reduce quantitive genetics to Mendelian genetics."

Putting up resistance

Despite its potential in exploring multigene traits like yield and storage quality, one of the first outcomes of the mapping exercise was the isolation of histidinol dehydrogenase, a plant enzyme responsible for herbicide resistance. Ciba's continued interest in this area may come as something of a surprise. Following comments from the Head of Ciba's Agricultural Division, Heimo Brunetti, about the ethics of herbicide-resistant plants, observers believed that the company would concentrate in the future on insect-and disease-resistance. However, Daniel Blancpain, Head of the company's Seeds Division maintains that "the combination of genetics and herbicides, allowing the use of more environmentally friendly herbicides" is still the likely first step for Ciba, at least in the U.S.: "then will come the disease-resistance." he adds.

One of Ciba's most exciting disease-resistance projects, according to John Duesing, is the cloning and expression in plants of a series of genes involved in fungal resistance. The discovery of the genes stems from work on understanding the mechanism of action of fungicidal chemicals. Certain compounds appear not to interact directly with the fungal pathogen but by inducing the induction of plants compounds that attack the fungus. A recent European patent application indicates that those compounds include lytic peptides and the enzymes, chitinase and glucanase "By inducing the expression of those genes, we can induce resistance," says Duesing.

Thus far, Ciba has evaluated a series of genes by expressing them constitutively both singly and pairwise in tobacco and then subjected them to pathogen challenge: synergies between distinct anti-fungal activities were noted. Although Duesing is enthusiastic about the project, he recognizes limitations: "The fungicide itself will induce 10-20 different genes. Compare that with the [genetic] induction of a single gene and you can see it's far more limited. However, in vegetative crops which are affected by one or two key pathogens, access to the genes could be important." Ciba will license the technology to get the genes into those crops. In a related project, Ciba is evaluating work from Jesse Jaynes at Louisiana State University in which microbial resistance genes from insect sources have been engineered into plants.

As in its healthcare business, there is no evidence of a "not invented here" in Ciba's agricultural activities. One illustration of that is in its development of diagnostic tests for plant diseases. At the beginning of 1992, the company launched a monoclonal antibody-based diagnostic test developed with Agri-diagnostics Associates for the wheat fungal pathogen *Septoria triticii* and that may be followed soon by tests for *Mycosphaerella* spp. Another recent link-up has extended Ciba's involvement in plant protection against nematodes. In February 1992, Ciba agreed to fund R&D at Biosys (Palo Alto, CA) for two years to the tune of $5 million. In exchange, Ciba gets the exclusive rights marketing rights for the resultant agents in markets outside the U.S. to add to rights in the U.S. already negotiated in 1991 with Ciba's American subsidiary.

Thence to market

In agriculture, says Daniel Blancpain, "The winner is the [company] that can bring solutions to the farm in the form of integrated pest management. Ciba's philosophy for success in agriculture is to combine its chemical and biological technological approaches with its position in the market: We know field crops—we are organised in the market. We will offer both seeds and chemicals but not as a package. The seeds business depends on bringing crop solutions." Global activity is a key component of Ciba's strategy both in agriculture and healthcare: interest in technology wherever it is generated, access to markets wherever products can be sold.

If Ciba-Geigy is typical (and that will become clearer from subsequent *Bio/Technology* profiles), then the top rank pharmaceutical and agri-business companies are all probably spending 0.5-1.0 percent of sales on biotechnology R&D. Multiply that figure by the turnover in those industries and you get the best possible response to carping small company CEOs who opine on the geography of biotechnology: biotechnology R&D—$700-1000 million worth of it a year—is happening all over the developed world—without hype, indeed with barely a whisper—in the multinational majors.

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