Venture Capitalists Push Designer Drug Start-ups

The money-men are putting together a new generation of biotech companies with researchers from disparate disciplines

EARLY LAST YEAR, a remarkable meeting took place at the Charles Hotel in Cambridge, Massachusetts. In a conference room, venture capitalist Chuck Hartman of the CW Group in New York assembled nine leading Harvard and MIT scientists, drawn from biology, chemistry, computer science, and artificial intelligence. Although they barely understood each other's work, Hartman told them he wanted them to form a company together to design "billion-dollar drugs." And much to his delight, they agreed.

Today, that company—Arris Pharmaceutical Corp.—is becoming a reality. It is taking shape in South San Francisco under the supervision of its new president, Michael J. Ross, a chemist and molecular biologist by training who left a top research position at Genentech in June. With about $10 million and a consulting group of 12 Ph.D.'s in chemistry, biology, and computer science, the company plans to use a Thinking Machine parallel processor and cutting-edge artificial intelligence software to design drugs. Their first project is an ambitious one: a pill to reduce cholesterol that can be taken orally under the prescription of a physician.

In these ways Arris represents the wave of the future in biotech start-ups. Compared to the firms that came into being in the late 1970s and early 1980s, this new generation is being shaped more directly by venture capitalists who are playing a bigger and more aggressive role than ever before in the makeup of their startups. Cutting-edge scientists are still disproportionately involved, but this time around they more often come from different disciplines in an effort to bring their various skills to move hot science from the lab to the production line more quickly than ever before. And rather than going for well-understood large molecules, these new firms are concentrating on a battery of small peptides and peptide mimics that promise a bigger payoff—but also require more innovative science and technology.

"There's a real niche—a real need for new research tools in drug discovery," says Ross, whose career parallels the transition from the first to the second generation of biotech companies: he was the third scientist to join Genentech soon after its start 14 years ago. And that new niche is being discovered at a time when, in the face of stagnation in most of the rest of the U.S. economy, more money seems to be flowing into medical and biological start-ups.

A leading survey released in July concludes that venture capitalists invested more money in medical and health care start-up companies in 1989 than in any other single area, surpassing for the first time such traditional startup investments as computer software, computer hardware, and electronics companies. "It turns out that last year, venture capitalists invested $469 million in 198 medical or healthcare companies," says Steve Galante, vice president of Venture Economics in Needham, Massachusetts, which published the survey. And among Galante's list of startups is a substantial proportion of new pharmaceutical firms.

The elements responsible for the birth of this second generation of biotech firms are both economic and scientific. The biotech business recently passed a threshold of profitability, with some recombinant drugs, such as Amgen's erythropoietin (EPO) and Genentech's human growth hormone, earning more than $100 million annually. Even if a company hasn't marketed a profitable drug yet, some have amassed appealing teams of scientists, making them targets for mergers or takeovers by large drug companies—a case in point: Eli Lilly's move to collaborate with Athena Neurosciences, Inc. in 1988, only a year after the company was founded to design drugs that could cross the blood-brain barrier and treat diseases such as Alzheimer's.

And that has turned the tables in recent years. Instead of scientists begging for money, in some instances, the investors have sought out the scientists. Hartman says it took him a year to identify the scientists he wanted to comprise the advisory board for Arris. And his is not the only such story. Kevin Kinsella of Avalon Ventures spent 2 years striving to lure Joshua Boger from his job as director of basic chemistry at Merck & Co. to found Vertex Pharmaceuticals, Inc. in Cambridge—Kinsella even enlisted the support of Boger's former thesis adviser at Harvard in his eventually successful campaign.

Scientists, for their part, are cooperating, because they see the overriding logic of putting together different disciplines in a commercial setting, just as they would in a hot new lab. Further, their interest is piqued by the scientific challenge being put forth: to pass on known molecules, such as making recombinant versions of insulin and growth hormone, and go after small designer molecules—custom-made peptides and peptide mimics that inhibit enzymes, and small organic molecules that trigger receptors for a remarkably specific response.

"An area that's hot right now is how cells traffic," says Brook Byers, a veteran venture capitalist who helped put together the funding for Genentech and Arris. Byers says that questions that are "big in the nineties" include finding out how lymphocytes know how to migrate to a specific place, how cells align themselves in tissue organization, and how they metabolize. Once researchers an-

Company	Date founded	Financing	Founders	Future products
Arris Pharmaceutical Corp. South San Francisco, CA	1989	Seed money of $372,000. About $10 million to date.	Venture Capitalist Chuck Hartman of C.W. Group and nine biologists, chemists, and computer scientists from MIT and Harvard.	Develops computer-enhanced peptide drugs, such as one to regulate the uptake of cholesterol.
Athena Neurosciences, Inc. South San Francisco, CA	1987	Seed money of $500,000. About $13 million to date.	Investor Kevin Kinsella and Dennis Selkoe, professor at Harvard University	Synthetic drugs that inhibit the enzymes that lead to plaque buildup in Alzheimers' disease and to regulate the transport of molecules across the blood-brain barrier.
Icos Seattle, WA	1989	$33 million.	Robert Nowinski of Genetic Systems, Christopher Henney of Immunex, and George Rathmann of Amgen.	Synthetic drugs to control the inflammatory response at specific sites.
Vertex Pharmaceuticals, Inc. Cambridge, MA	1989	$13.3 million to date.	Joshua Boger, formerly of Merck	Synthetic drugs to suppress the immune system and to treat viruses.

swer those questions, they will offer obvious opportunities for designing drugs to block or enhance those functions—in precise ways.

These new firms aren't alone on the playing field, of course. First-generation firms are gearing up to design small molecules, too. But the start-ups' strategy for getting out of the shadow of established firms lies in fresh ties to leading academics, scientists with the stature to attract investors. At Arris, the scientific advisory board includes all nine who were in the hotel room in Cambridge with Hartman, including such academic heavyweights as chemist George Whitesides of Harvard; Patrick Winston, head of MIT's Artificial Intelligence lab; and Harvey Lodish, Eric Lander, and Peter Kim of the Whitehead Institute.

Icos in Seattle brought together three veterans of early biotechnology firms including Robert Nowinski, the founder of Genetic Systems; Christopher Henney, founder of Immunex; and George Rathmann, the chairman of Amgen. Icos's combination of talent has already paid off: The firm opened its labs earlier this year with an unprecedented $33 million financing package.

But after capital and casting comes product. If the new companies are to succeed, they are going to have to move science from the lab to the factory faster than it has ever been done. Which is why most of the new firms are starting with specific products in mind.

Icos, at less than a year, has received considerable attention for its plans to design small molecules that would work like adhesive proteins to control the inflammatory response, say, to treat muscular sclerosis and rheumatoid arthritis. And Arris is working on drugs based on a paper published in *Nature* only last February. In it, MIT biologist Monty Krieger described how scavenger-cell receptors help build the plaque that causes arteriosclerosis. The Arris team, with Krieger as a consultant, plans to identify natural compounds that bind to the receptors, then use artificial intelligence computing programs to find out what features those compounds have in common. They hope their computer database will help them come up with the optimum design for a synthetic peptide that could be used to block the receptor to prevent arteriosclerosis—in effect, an anti-cholesterol pill.

These are the dreams of which money—and bankruptcies—are made. The seed money hurdle is in some ways the easiest. Says Byers about the financing needs these start-ups will experience in the all-too-near future: "I'm afraid it's easier to raise money to start them than to sustain them." Nowinski agrees: "You have to understand that companies die because they're undercapitalized—not because the science isn't good enough. The elements that create a successful company are the degree of capital and the aggressiveness of the company to be able to pursue its ideas." Aggressiveness and one winning idea are what the money-men are counting on. Says Hartman: "As a venture capitalist, I want to start a company whose scientists can design a small molecule that is orally active and specific enough for a primary care physician to prescribe for outpatient use. Those three things add up to a billion-dollar profit." ■ ANN GIBBONS

Justice Department Joins Whistle-blower Suit

The Justice Department last week announced it was joining forces with a whistleblower in a complaint against a federally funded researcher accused of scientific misconduct. If the suit is successful, the government could recover three times the $1.3 million in grant money awarded to John L. Ninnemann, a researcher formerly at the University of Utah and the University of California at San Diego. The case marks the first time the government has intervened in a so-called "qui tam" suit involving scientific misconduct.

Qui tam suits originated with the False Claims Act in 1863, a law intended to discourage unscrupulous businessmen from defrauding the Union Army by giving financial incentives to private citizens who spot the frauds. Under the act, a whistleblower may receive up to 30% of the money recovered when qui tam suits are successful. Congress amended the act 4 years ago to make it easier for potential whistle-blowers to step forward, and since then 259 suits have been filed, mostly against defense and health care contractors.

Many scientific organizations have expressed concern that a dramatic shift in the way scientific misconduct cases are handled could take place should qui tam suits proliferate in the realm of science. Investigations would be taken over by the justice system, and, they argue, lawyers and judges, not scientists, would become the final arbiters of whether scientific misconduct has occurred (*Science*, p. 802, 16 February).

Unless a pretrial settlement is reached, that could be the fate awaiting Ninnemann. The case against him involves research on the treatment of burn victims. In 1983, his University of Utah lab technician J. Thomas Condie claimed Ninnemann had published false information in scientific journals and presented false information at a scientific meeting. Condie claims an initial internal investigation by the university failed to agree with his charges, and he says he was asked to resign from his technician job.

The next year, Ninnemann transferred to the University of California at San Diego. Condie continued to pursue the case, ultimately teaming up with Eugene Dong, a Stanford University faculty member who holds degrees in both medicine and law. Together they uncovered additional evidence they felt proved Ninnemann's guilt. After receiving this new evidence, the University of Utah conducted a second investigation of Ninnemann in 1987. This in turn led to an investigation by NIH, and one by UCSD. Utah officials will not speak about the case, nor will NIH officials. Gerard N. Burrow, UCSD vice chancellor for health science, issued a statement saying that a 1988 faculty committee asked to examine Ninnemann's work "concluded that there was no evidence of intentional misrepresentation or fraud. We have no reason at this time to question the committee's conclusion."

But even if these investigations had blasted Ninnemann, Dong says the government would still be out the $1.3 million it gave Ninnemann for his research. So in September 1989, Dong and Condie tried a new approach. They filed the qui tam suit to recover the government's grant money, claiming that Ninnemann had made numerous misstatements in his NIH grant applications.

In announcing its decision to join the suit, assistant U.S. attorney general Stuart M. Gerson said, "The government's action in assuming responsibility for the case reflects our insistence that scientific research, especially when federally funded, be truthfully reported." Gerson said the government was seeking reparations not only from Ninnemann, but also from the two universities which had certified that the information in grant applications and progress reports was true.

Ninnemann, who left UCSD in 1988 and is now a faculty member at Adams State University in Alamosa, Colorado, declined to comment on the case. ■ JOSEPH PALCA