Schering-Plough, has a similar *p53*-carrying adenovirus in human trials. So far, neither the Schering-Plough nor the Introgen viruses have caused any troublesome side effects, and while Schering declined to comment on the effectiveness of its virus, Introgen reported that tumors have regressed or at least stopped growing in some patients treated with the virus alone or together with the drug cisplatin. Based on those results, Introgen, in collaboration with RPR Gencell, a division of the French drug company Rhône-Poulenc Rorer, has just begun a larger trial aimed at evaluating the treatment's effectiveness for head and neck cancers.

Other efforts focus on knocking out the function of the oncogene *bcl-2*, an inhibitor of apoptosis, which is overactive in about half of all human cancer types. "Cells with upregulated *bcl-2* ... are very difficult to kill with anything you throw at them," says cell-death researcher John Reed of the Burnham Institute in San Diego. Several companies are trying to develop drugs to inhibit the Bcl-2 protein, says Reed, while others are already testing a more direct assault on Bcl-2: antisense nucleotides designed to prevent the protein from being made in the first place.

In April, Andrew Webb of the Royal Marsden Hospital in Sutton, Surrey, in the United Kingdom, and his colleagues reported the results of the first human trial of anti-*bcl-2*, in nine patients with advanced non-Hodgkin's lymphoma. One patient had a complete remission and another had partial reduction of his tumors. Based on the promise of those results, medical oncologist Howard Scher of Sloan-Kettering in New York, along with the San Diego antisense biotech company Genta, which developed the drug, are waiting for FDA approval to begin testing it in 10 to 20 patients with a variety of solid tumors that overexpress *bcl-2*.

Once the roadblocks along the suicide pathway have been removed, says Reed, it may be necessary to trigger apoptosis by damaging the cells. As a result, he says, efforts to restrain *bcl-2* or replace *p53* may be most effective, he says, when used "as a sensitizer in combination with traditional cytotoxic therapies."

Although traditional therapies are likely to remain a part of the anticancer armamentarium, the new approaches could transform treatment strategies. If even a few of them pay off, they may mean a future in which doctors will screen tumors for the mutations they carry, then target the defects in the cancer cells directly to prime the tumor cells for killing. "It won't matter whether it is a breast, ovarian, or prostate tumor," says Peter Hirth, executive vice president for research and development at Sugen. "[The mutation] will be the target for therapeutic intervention."

–Marcia Barinaga

BIOTECHNOLOGY BUSINESS

On the Biotech Pharm, a Race To Harvest New Cancer Cures

More than 1400 biotechnology companies make their homes in North America, according to the investment newsletter *Biotech Navigator*, yet fewer than 50 biotechnology products have been successfully commercialized to date. With statistics like that, it's easy to see why biotech has gained a reputation as "one of the worst investments on the street," in the words of David Tomei, founder and chief executive officer (CEO) of the Richmond, California, firm LXR Biotechnology Inc. Yet the former Ohio State University pharmacologist is among a cadre of scientist-entrepreneurs who believe they can reverse that reputation—by developing drugs that remedy the genetic and molecular defects behind most cases of cancer.

But will tapping into this revenue stream be any easier for these new firms than for many of their predecessors in biotech? Tomei and others say yes, because companies such as LXR aren't merely applying ideas developed by academic scientists, but are generating many of their own advances in basic cancer biology. That kind of innovation "will succeed in reversing the feeling that biotech was wishful thinking," says Tomei. Still, any new molecular oncology company faces other hurdles that have tripped up many biotech companies before, leaving them cashless and without a product to sell.

A SAMPLING OF MOLECULAR ONCOLOGY FIRMS

Company (Location)	Type of Product	Status
Calydon (San Francisco, CA)	Prostate cancer gene therapy	Preclinical testing
Canji/Schering-Plough (San Diego, CA)	*p53*, *RB* gene replacement therapy	Early clinical trials
IDUN Pharmaceutical (San Diego, CA)	*bcl-2* inhibition	Preclinical testing
Incyte (Palo Alto, CA)	Gene sequence databases	19 subscriptions sold
Introgen Therapeutics (Austin, TX)	*p53* replacement therapy	Early clinical trials
Genta (La Jolla, CA)	Antisense *bcl-2* inhibition	Early clinical trials
LXR (Richmond, CA)	Antiapoptotics	Advanced clinical trials
Mitotix (Cambridge, MA)	Cell cycle inhibitors	Preclinical testing
Myriad Genetics (Salt Lake City, UT)	Genetic testing	BRACAnalysis kit
Onyx (Richmond, CA)	*p53* gene therapy	Early clinical trials
Ribozyme (Boulder, CO)	Growth factor inhibition	Preclinical testing
Targeted Genetics (Seattle, WA)	*HER2* gene therapy	Advanced clinical testing

The goal of this new effort in "molecular oncology" is to devise drugs that correct the specific defects that cause cancer in the first place—the abnormal activation of growth-promoting oncogenes, for example, or loss of tumor-suppressor genes. The hope is that treatments will turn out to be more effective and have fewer side effects than conventional cancer chemotherapeutic drugs (see p. 1036). More than two dozen firms, with a combined capitalization in the hundreds of millions of dollars, are competing for leading positions in this emerging market.

The potentially huge profits available to the inventors of better cancer drugs explain their eagerness. The American Cancer Society estimates that 1.4 million new cases of cancer will be diagnosed in the United States in 1997, with the overall medical costs from cancer amounting to $35 billion. Of the world's eight top-selling anticancer drugs, four—the prostate cancer drugs Casodex, Eulixin, Lupron, and Zoladex—are merely palliative, yet have combined annual sales of $1.7 billion, while sales of the breast cancer drugs tamoxifen and taxol are approaching $500 million and $800 million, respectively.

To avoid this fate, a new company must have a scientific advance that promises a practical treatment. It must beat out competitors for precious start-up capital and find revenues to supplement that capital during the protracted process of preclinical and clinical testing. It must protect its intellectual property, and if it raises money by agreeing to share scientific advances with larger pharmaceuticals firms—a standard practice among young biotech firms—it must actually deliver the goods.

For the many cancer researchers who, like Tomei, have left academic posts to seek their fortunes in biotech, there's a clear message: Bucking the biotech trend won't be simple. "If you have a great idea, solid science, and

earthshaking discoveries, you are still only 10% of the way there," Tomei admits.

Because the best available strategies against tumors—poison them, burn them, or cut them out—are such blunt instruments, therapies that counter cancer where it starts, with the alteration of genes whose job is to promote or limit cell growth, have an enormous attraction to cancer victims and entrepreneurs alike. "Cancer is going to be treated as a genetic disease," says Thomas Needham, director of business development at Mitotix Inc., a Cambridge, Massachusetts, biotech firm that is applying its knowledge of cell division in yeast to develop novel drugs aimed at halting the inappropriate cell proliferation that is the hallmark of cancer. "That plays to our favor, because the current modes of therapy are not great."

New targets. Many investors apparently agree. Ten venture capital firms, for example, have invested more than $23 million in Mitotix, founded by cell-cycle researchers David Beach of Cold Spring Harbor Laboratory in New York state and Giulio Draetta of the European Institute of Oncology in Milan. "The original focus was on cell division in yeast, and Mitotix was taking a high-risk bet on the applicability of this to human cancer," says oncologist Jason Fisherman, a partner at one of the venture capital firms, Boston's Advent International. "[But] the company has the molecular, cellular, and genomic tools to continue to develop new targets [for anticancer drugs]. These companies are fundamentally discovery companies—engines for churning out molecular targets."

Because targets, not profits, are all a new biotech company is likely to churn out for several years, the central challenge for molecular oncology companies is simply to stay in business until revenues exceed losses. And while each firm has its own unique business strategy, it's possible to spot a few patterns in the noise.

One approach most firms deliberately avoid today is to go it alone—to try to become a "fully integrated" biopharmaceuticals company that develops drugs all the way from discovery to testing, manufacturing, approval by the U.S. Food and Drug Administration (FDA), and marketing. A few big biotech firms such as Genentech, Amgen, and Genzyme have successfully shot these rapids, although not with compounds that treat cancer. And Cell Pathways Inc., a privately owned molecular oncology firm with laboratories in Aurora, Colorado, is attempting the same feat. Its lead product, a compound called FGN-1 that induces programmed cell death selectively in precancerous cells, is already in phase III clinical trials, and the firm is now on the verge of its initial public offering of stock. But few firms can afford the infrastructure full integration requires, and most are therefore aiming to be something less than the next Amgen or Genentech.

A far more common—indeed, almost obligatory—path for young molecular oncology firms is to form partnerships with big pharmaceutical firms. For example, under a collaborative agreement, the German firm BASF Pharma will pay up to $48 million for Mitotix's help in developing drugs that inhibit cdc25 phosphatases, enzymes discovered by Beach that are essential for cell division and may be hyperactive in cancer cells proliferating out of control.

In such arrangements, the biotech partners get the money they need to stay afloat and are freed from the expense of testing and marketing candidate drugs, while the pharmaceutical partners are freed from the high risk of failure inherent in the early drug-discovery process. But such collaborations do

GRAHAM G. RAMSAY

Sell division. Scientists at Mitotix seek drugs to block inappropriate cell proliferation, cancer's hallmark.

have a downside. The pharmaceutical companies usually pay only part of their commitment up front, with the rest coming in chunks later, on the condition that the collaboration reaches certain milestones by certain dates—for example, entering clinical trials or filing for FDA drug approval. That creates deadline pressure and limits the number of creative ideas a small biotech firm can afford to explore. It's for precisely these reasons that Advanced Cellular Diagnostics, an Elmhurst, Illinois–based biotech firm developing drugs that would arrest the growth of cancer cells by turning up expression of the tumor-suppressor genes *p53* and *p21*, has avoided partnerships, says molecular biologist Sarah Bacus, who founded the company with proceeds from the sale of a previous venture. "We try to meet our own internal milestones, but we don't have to answer to anyone, and therefore we can work with a lot of different therapeutics," Bacus says.

Another way for a small biotech firm to reduce financial worries while remaining relatively independent is to sell out. The San Diego–based biotech firm Canji Inc., for example, became a wholly owned subsidiary of one of its former collaborators, pharmaceutical giant Schering-Plough, in 1995 at a cost to Schering of $55 million. And although the deal has meant a loss of autonomy for Canji—"The decision-making process is a little bit slower, since you can't just run upstairs and talk to the boss," says Dan Maneval, Canji's director of pharmacology—the arrangement has been mutually beneficial, both he and Schering-Plough officials say.

Data in the bank. An entirely different way to make money in molecular oncology, Advent's Fisherman points out, is to offer tools instead of targets. "Small companies don't have to discover drugs themselves to be successful," he says. He points to Myriad Genetics, based in Salt Lake City, Utah, and Incyte Pharmaceuticals, of Palo Alto, California, which sell information about the genes that cause cancer and their patterns of inheritance in the population, rather than potential therapies. Myriad is already marketing BRACAnalysis, a test for mutations in the *BRCA1* and *BRCA2* genes recently linked to hereditary breast cancer, and has plans to develop other potentially lucrative diagnostic products.

And Incyte, unlike most small biotechs, is already turning a profit with its LifeSeq database of gene sequences and gene expression patterns. LifeSeq brought in $12.2 million in pharmaceutical company subscriptions in 1995, $42 million in 1996, and $39 million in the first half of 1997 alone, according to CEO Roy Whitfield. "These databases cover all medical research applications, but we put in them what the drug companies want to see, and I can tell you that oncology is what they are most interested in," Whitfield says.

But survival in the crowded world of molecular oncology may depend as much on luck as on scientific and financial savvy. For example, Cell Pathways, one of the firms closest to actually marketing a cancer-prevention therapy, has benefited from the serendipitous fact that its cell-death activator FGN-1, which has been shown in preliminary clinical trials to prevent precancerous colon polyps from becoming fully malignant, is a metabolic byproduct of the anti-inflammatory drug sulindac. That may significantly speed trials of the drug's safety, because "it's been floating around in human bloodstreams for years and already has a bit of a track record," according to gastroenterologist Rifat Pumukcu, the company's scientific founder.

With such advantages, a few molecular oncology firms will sooner or later pull ahead of the pack, concludes Canji's Maneval. "It's going to be difficult to have all two dozen companies move along together forever. There's going to be a weeding out, and [those with] the good technologies"—plus good fortune—"will prevail."

–Wade Roush