

Coming of Age

The biotech industry is revolutionizing the business of drug discovery and is turning out products that have transformed medicine.

IF THERE IS ONE THING

that is certain about biotechnology, it's that the industry doesn't think small. In just a few decades, biotechnology has come to mean big risks, big rewards, and increasingly big business. Last year, revenue for publicly traded biotech companies totaled \$52.7 billion, according to Standard & Poor's June 2006 industry survey—up 22% from the previous year. Five drugs—Enbrel and Remicade for rheumatoid arthritis, Procrit and Aranesp for red blood cell enhancement, and Rituxan for B-cell non-Hodgkin's lymphoma—each saw sales top \$3 billion.

But biotechnology can mean big contradictions too. While the top ten companies accounted for almost two-thirds of last year's revenue, most biotech firms still lose money. And even as new technologies bring more innovative, powerful drugs, the development process remains long and costly—too long and costly for the companies, the Food and Drug Administration, and, most important, the patients. But recent advances and new initiatives mean that we may soon see the big payoff of biotechnology without the big wait.

That's good news because the science of biotechnology is more promising than ever. One of the most exciting new developments is the use of fully human monoclonal antibodies. They are proteins that can detect and bind themselves to a specific substance in the body, triggering an immune response—potentially a powerful tool to fight cancer. Monoclonal antibodies date from the mid-1970s, but the problem was that they were made in mice and rats, so the antibodies—looking foreign to the

human body—would themselves be targeted by the immune system, restricting their usefulness. In the past decade, however, techniques have been developed to keep mouse protein out of the antibody. The result: an antibody that looks fully human to the body.

RIGHT ON TARGET

Using these “humanized” antibodies, scientists can now attack cancer and other diseases with biological substances instead of chemical compounds. There are big advantages to using biologics instead of chemicals. While monoclonal antibodies can be extraordinarily specific, homing in on one substance and attacking it alone, chemicals often take a more shotgun approach, resulting in side effects. “Monoclonal antibodies are a natural mechanism, so in many cases they’re ideal,” says Kurt Gehlsen, vice president and chief scientific officer at Research Corporation Technologies, a Tucson company that provides early-stage funding for biomedical technologies. “Now that we can humanize antibodies, they’re back in a big way.”

At Amgen Inc., the world’s largest biotechnology company, fully human monoclonal antibodies have enabled the development of innovative new oncology drugs. While Amgen has a long history of making products that attack the symptoms of disease and the side effects of treatment, (the infections and anemia that can often keep patients from getting crucial chemotherapy), its new drugs attack the disease itself. “In the last five or six years we’ve made a big push to bring targeted therapeutics to market,” says Joe Miletich, Amgen’s senior vice president for research and development.

One of the company’s most promising drugs, panitumumab, is a fully human monoclonal antibody that attacks various types of solid-tumor cancers. “Because it’s fully human, the body recognizes it as a protein that the body itself makes, so there is no reaction against it,” says Miletich. “This is important, because it lets us develop new therapies that are targeted to specific diseases and at the same time produce fewer side effects.”

Amgen, which spent \$2.3 billion on research and development in 2005 and expects to spend some \$3 billion this year, is also using fully human monoclonal antibody technology for denosumab, a drug to arrest bone loss. Currently in late-stage trials, with more than 10,000 patients using it, denosumab blocks a protein—known as RANK Ligand—that plays a key role in

the breakdown of bone. It is a completely new way to attack the problem. “For the first time we have the potential to control the rate of bone loss over a range of diseases, including cancers and osteoporosis, with a biological mechanism,” says Miletich, who expects denosumab to be on the market by the end of the decade.

It’s not just the drugs that are getting better either. New tools have given researchers powerful ways to analyze and measure the effects of experimental treatments. “Now we have imaging tools that let us see what’s going on in people in real time—and these tools are all non-invasive,” says Miletich. “We can tell what a tumor looks like based on its metabolism. We can see how it’s using its fuel source, and if it’s using less, which tells us the treatment is working. Before, if we wanted to see how a tumor reacted to a treatment, we’d have to take a crude X-ray or cut into the patient.”

BECOMING MORE PREDICTABLE

Yet biotechnology’s toolbox needs to get better still. Developing a new drug is a staggeringly expensive and lengthy process. The average drug takes between \$800 million and \$1.7 billion, and 12 and 15 years, to develop, according to the Pharmaceutical Research and Manufacturers of America. Meanwhile, nine out of ten experimental drugs fail in clinical trials because of the difficulty of predicting how they will behave in humans. The result is that life-saving medicines are slow to hit the market, and when they do arrive, they often have a hefty price tag. The long time and big money required to bring a drug to market are major factors behind Big Pharma’s biotech buying spree: Acquiring a biotech company means access to products well along in development.

The challenge, then, is to develop better ways to predict early on how drugs will work in humans. That will enable safe, effective medications to get to market faster, while weeding out inferior products before a lot of time and money are sunk into them. To this end the FDA has launched its Critical Path Initiative, an effort to identify and sponsor research projects to create tools for more efficient drug development. One promising area involves the creation of biomarkers—measurable characteristics in animals and humans that help predict the effectiveness of a drug. Under the Critical Path Initiative, the FDA and the biotech industry are already collaborating to develop biomarkers for liver toxicity—a common reason drugs fail in human trials but a side effect that is only recognizable after extensive clinical testing. Projects like this, and the new tools and tests that result from them, will make sure the breakthroughs in the lab break through to the market. ■

New tools have given researchers powerful ways to analyze the effects of experimental treatments.



The Big Picture

An insiders' look at how the biotechnology marketplace is evolving.



Our panel of experts (left to right): BIO's Greenwood; Euclid's Jones; Leff of Warburg Pincus, and Tullis of Tullis-Dickenson

Science may be the star of biotechnology—the technical knowledge and breakthroughs that have brought us miracle drugs and life-saving therapies. But, as with any big production, plenty of factors behind the scenes can make—or break—a blockbuster. No doubt, biotech is capable of making our lives better, brighter, and longer. But when and whether new products come to market depends as much on economic incentives, regulatory schemes, and intellectual property protections as it does on innovation.

Where is biotechnology heading? For insight on the potential of the industry and the pitfalls it faces, FORTUNE Custom Projects hosted a roundtable with four of the field's leading market experts: James Greenwood, president and CEO of the

Biotechnology Industry Organization (BIO), which represents more than 1,100 biotechnology companies and institutions; Elaine Jones, Ph.D., general partner at Euclid SR Partners, a venture capital fund that focuses on IT and life sciences; Jonathan Leff, managing director of Warburg Pincus, a private equity firm with investments in biotechnology; and Jim Tullis, CEO of Tullis-Dickerson & Co., a health-care-focused private equity firm. Here are excerpts:

Moderator: Biotech, once the new kid on the block, now has 230 approved drugs on the market in the U.S., with 50 more drugs awaiting final approval. How has the industry matured?

Leff: It's continuing to be a major source of innovation. But biotechnology

companies today are integrated across the value chain and are commercializing products with sales and marketing infrastructures. The industry is, in many ways, competitive to Big Pharma.

Tullis: But I think the financial picture has become a little more complex. The number of successful, profitable companies is a relative handful compared to the number of companies in total. There is investor confusion, and that's led to relatively low valuations, which has backed up into an unusual phenomenon: There have been some 50 IPOs in the last five or six years, but a lot more public companies have been acquired, resulting in a net diminution in the number of freely standing, freely traded public biotech companies.

Moderator: What are the hot niches in the industry?

What breakthroughs are emerging from the R&D departments of leading-edge biotech companies?

Greenwood: The general trend is toward personalized medicine—the ability to understand our genetic predisposition to diseases and then to target therapeutics toward specific gene traits. It's going to give us a greater ability to predict, and prevent, diseases.

Tullis: Cancer is still No. 1. I think that we, as a society, don't recognize how significant the effort has been in finally causing cancer deaths to decline, which is a very big milestone in history. Other areas are growing very quickly, too, like diabetes. There was a lot of press recently about GLP-1 and the fact that if you have adult-onset diabetes, you can take this drug and feel better than you feel

with insulin, and lose weight. That's a big deal. Another area that's very big is personal diagnostics. We are seeing the first market entry of products that help decide whether you should have chemotherapy, radiation, surgery, or a combination of those treatments.

Jones: There are two other, more basic nuts-and-bolts things going on. We've been making drugs for a very long time, but we still don't have a great understanding of what makes one drug more bioavailable—that is, absorbed and used by the body—than the next, or how to target it to certain parts of the body. So there's a lot of work being done to understand this. Secondly, when we dose animals or humans and we see no effect, sometimes we don't know whether that's because we haven't given enough of the drug or because the drug hasn't gotten where it's supposed to go. And so there are new types of techniques—imaging, micro-dosing—that can help us say that the “no effect” was really no effect; that the drug is at the receptor where it's supposed to be—it's binding, it's triggering a biological effect—but it's not modifying the disease. Then we'll know that this target is not going to be of use to us in treating this disease, and we can go on to the next promising target.

Moderator: Is the time frame from initial research to commercialization of biotech products increasing or decreasing? And how is the industry responding to the trend?

Leff: In general, it is increasing. One major reason is that much of the low-hanging fruit—the obvious approaches to disease, like using insulin to replace the lack of insulin in diabetics—are gone. More and more of the drugs that biotech companies are developing are novel drugs with new mechanisms, where the disease biology is not fully understood. Those are more challenging and time-consuming, not only because you have to figure out the disease and how your drug is acting as you go, but also because there is not an established regulatory framework.

Greenwood: The reality is that it still takes eight to ten years from discovery to commercialization. The FDA and others have recognized that we really need to do a better job than that. The Critical Path Initiative is very, very important because it looks for ways to reduce the time period significantly.

Moderator: What is the Critical Path Initiative and how long has it been in place?

Greenwood: It's really brand new. It's an FDA addition introduced in 2004. They recognize that there

are a host of discoveries that are constantly being made, yet there is a slowdown in getting those products to market. So they've just announced that they will fund 76 research projects that hope to shorten this time frame in a whole host of ways. Projects like the development of better evaluation tools—biomarkers and disease models. Part of the issue here is funding. President Bush has asked for \$6 million. We'd like to see significantly more dollars invested in the effort. It will pay off.

Moderator: Are there specific areas, technologies, or diseases that companies and investors are increasingly focusing on because they see a quicker path to ROI?

Tullis: Personal diagnostics is a field where the

path from inception to having a licensed product on the market is faster than it is for a therapeutic, for a lot of obvious reasons, including the risk to the patient. Having said that, it's still complex. It still takes a lot of investment and a lot of time. You might be talking three, four, five, six years as opposed to talking eight or ten years.

Jones: I think those diagnostics, paired with some type of therapeutics, are likely to be the ones where you see the first interest. General diagnostic companies are still not quite in the hot spot today, regardless of all of the emphasis on personalized medicine. But I do see lots more plans coming, and I see more interest. So I do believe it will be a future trend.

Biotech Pioneer

PDL BioPharma, Inc., is a biopharmaceutical company focused on discovering, developing, and commercializing innovative therapies for severe or life-threatening illnesses. We currently market and sell a portfolio of leading products, Cardene® I.V., Retavase® and IV Busulfex® in the acute-care hospital setting and generate royalties through licensing agreements with top-tier biotechnology and pharmaceutical companies based on our pioneering antibody humanization technology. Currently, PDL's diverse late-stage product pipeline includes six investigational compounds in Phase 2 or Phase 3 clinical development for hepatorenal syndrome, inflammation and autoimmune diseases, cardiovascular disorders, and cancer. PDL BioPharma is committed to developing and

commercializing innovative acute-care treatments for patients suffering from severe or life-threatening diseases.



Leff: The traditional path to success has been therapeutic products. Everyone knows that the percentage of products that succeed, among those put into clinical development, is only 10% to 20%. But delivering therapeutics has still been a business model that has created sustainable, durable value for investors, because there is a great willingness, in this country in particular, to pay for drugs that can treat diseases in a way that makes a difference. That enables companies to take risks and get into long development programs. One of the key issues for the diagnostics industry is whether diagnostics that are important can sustain pricing that looks more like that of therapeutics. If they can, diagnostics will be a very important area for investment.

Moderator: There has been a lot of talk recently about patents and proposed revisions to the patent systems in the U.S. and abroad. How are current intellectual-property protections, or the lack of them, affecting the biotech industry?

Leff: There's tremendous uncertainty. If you go and retain—as we all do—the best patent lawyers in the country to determine if a company will be able to survive patent land mines and get its product to market, the answer, almost invariably, is that it's uncertain. We can handi-

cap the odds, but at the end of the day you can't predict what the Patent Office is going to do and you can't predict how the courts are going to treat individuals. That uncertainty is a major deterrent to innovation.

Jones: Intellectual property is at the heart of every transaction in the biotech industry. If we cannot be certain that patents are defensible and that we can practice them, the whole basis of capital infusion into this industry dissipates very rapidly.

Moderator: What reforms, then, are needed?

Leff: Clearer standards and more consistent application of them by the Patent Office are absolutely critical, but it's a tall, tall, order—the technology is so complicated and the number of patent filings continues to grow exponentially.

Greenwood: Very frequently there are protracted, expensive battles between inventors trying to prove who the first to invent was. If we move to a first-to-file patent system, we might be able to reduce those kinds of battles. Also, allowing the Patent Office to publish patent applications within 18 months after filing would enable competing companies to know what they're up against, and whether they're going down a

path that someone else has already claimed.

Moderator: Is stem-cell research an area for growth in the U.S. biotech industry? Is the answer to that dependent on the current administration in Washington?

Tullis: This is an enormously exciting field. And it's not something that is just ten years down the road. When you do a bone marrow transplant, you're transplanting stem cells. Where we are today is we're saying, "Okay, where else can we use stem cells? What types of stem cells work in different areas to grow an organ, to grow skin, to grow strength in the heart?" It is incredibly important for the U.S. government to be doing everything it can to stimulate and build this industry, because it's the future and we need to be there.

Moderator: What are the prospects for the industry through the decade and beyond?

Jones: I think the one area where we're clearly going to see an impact is in personalized medicine. The outcome of that may be earlier diagnosis of disease, which everyone recognizes will enable a much more effective intervention. It's the immediate fallout of genomics. We're going to know this stuff. We are going to know who is at risk.

Greenwood: I think it's safe to say that biotechnology will be the most transformational human endeavor in history. We will sequence the genomes of newborns; we will understand their genetic proclivity to diseases; and we will have therapeutics that will prevent those diseases from being expressed in the first place. In time the health-care system not only will figure out how to pay for these innovations, but will insist upon it. That's because it will be the smart thing to do. ■

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