The Rapid Rise of Biotechnology

LYNN C. KLOTZ '65

ALTHOUGH biotechnology as we know it had yet to come into existence while we were at Princeton, the key science underlying it—molecular biology—had been advancing nicely since Watson and Crick's discovery of the structure of DNA in 1953. In my view, it was César Milstein's invention of hybridomas, hybrids of cancer cells and other cells, to make monoclonal antibodies, and Herbert Boyer and Stanley Cohen's invention of recombinant DNA that mark the launch of biotechnology. Both happened more than a decade after we graduated. Biotechnology is the application of molecular biology and other sciences to practical, mainly commercial, ends. The two together I call the "new biology." The "other sciences" contributing to the rapidly advancing capabilities of the new biology amount to a big list: chemistry, physics, materials science such as nanotechnology, computer science such as bioinformatics, and some aspects of classical biology.

A major development, in 1964, was Robert Holley's first-ever sequence of a DNA or RNA molecule at Cornell University. It was a long and tedious undertaking. The molecule was alanine-transfer RNA composed of only 77 AUGC letters, a small molecule by gene and genome standards. Fast forward from then to now. Today it is routine to sequence a whole human genome of 3 billion AUGC letters in a few months starting from scratch and at a cost in the thousand-dollar range. This represents a spectacular advance in our capabilities. Among the many important things that rapid sequencing provides is the new field of personalized or precision medicine, which is improving our ability to pick the right drug to treat a patient's particular disease. In cancer therapy, for instance, employing the right drug the first time is very important, because you may not get a second chance.

Today biotechnology has permeated many fields of research and development from health care, to agriculture, to chemical manufacture, to food and beverages, to the environment, and to alternative energy and fuels. From the beginning, health care has been its biggest application in every nation. In the United States and Great Britain, 80 percent of the biotechnology effort goes to health care, mainly the discovery

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Lynn C. Klotz is Co-managing Director of Bridging BioScience and BioBusiness, a two-person biotechnology education company currently focusing on drug discovery and development. He is also Senior Science Fellow at the Center for Arms Control and Non-proliferation working on chemical and biological weapons control and on biosecurity.

and development of new drugs. Either agriculture or food and beverages represent the second largest application in most countries. Fast growing but still small fields include chemical manufacture and biofuels. As my late roommate Ed Sylvester remarked, chemicals can be manufactured through genetic engineering at the temperature of "a fine spring day."

In this essay, I take only drug discovery and development to show how we have advanced to where we are today. One thing we have learned along the way is that living organisms, even single-cell bacteria, are very complicated. It follows that understanding life at the level of molecules (molecular biology) for guidance in discovering and developing drugs is also very complicated. Moving in lock-step with advances in new biology science are the growth of the small-company biotechnology industry and major changes in the strategies of the big pharmaceutical companies.

TO understand recent developments, a little pre-biotechnology history is in order. The pharmaceutical industry cut its teeth on antibiotics. Alexander Fleming discovered penicillin by accident in 1928. He was not a chemist, so he didn't try to figure out its structure, how to synthesize it, or how to purify it. In fact, he abandoned his work on it. More than ten years later, Ernst Chain and Howard Florey figured out how to synthesize and purify penicillin, paving the way to the modern pharmaceutical industry. The three shared the Nobel Prize in Medicine. They deserved it as much as anyone who has ever received the award. Antibiotics have saved hundreds of millions of lives.

Once penicillin's effectiveness in curing bacterial infections was demonstrated, the flood-gates opened to identify other antibiotics. Antibiotic production launched the modern chemistry- and fermentation-based pharmaceutical industry, and was responsible for much of its huge financial success. In 1940, when Chain and Florey published their paper, *Penicillin as a chemotherapeutic agent*, Chain published another paper in another journal titled *An Enzyme from Bacteria Able to Destroy Penicillin*. So at the same time that penicillin was about to be launched commercially, antibiotic resistance was observed. The paper was likely more of a curiosity than a concern about resistance.

Until the early 1980s, antibiotics were a major focus for the pharmaceutical industry. But a huge business problem was emerging. Antibiotics had become a large-volume, low-price, low-margin, and very competitive business, with penicillin and tetracycline and their many derivatives widely available. Moreover, a patient takes an antibiotic for a week or two and the infection is gone, along with further sales to that patient. Unfortunately, most companies abandoned completely the discovery and development of new antibiotics just at the time when resistance was becoming worrisome.

Today antibiotic resistance is one of the most pressing public health problems facing the world. Most pathogenic bacteria are resistant to multiple antibiotics. We are possibly coming full-circle, returning to the time when people died from bacterial infections because there was no cure. We desperately need new antibiotics that work by new mechanisms. Some companies are now returning to antibiotic discovery, both because of the need and because curing antibiotic-resistant infections can cost well over $50,000, so there is ample margin to charge high prices for new antibiotics and still achieve cost-effectiveness.

Pharmaceutical companies were seeking new strategies and new markets. Focusing on chronic conditions such as arteriosclerosis and depression promised to provide captive patients who would take medicines continually throughout their lives. As a testimony to the value of this strategy, Pfizer's high-cholesterol drug Lipitor had $13 billion sales in 2011, the last year before its patent term ran out. This was the largest ever annual drug sales at the time.

The rapidly advancing capabilities of the new biology spawned a number of other changes. Big pharmaceutical companies began to shift their discovery efforts from chemistry to molecular biology. Hundreds of small biotechnology companies were born, some eventually to join the ranks of big pharmaceutical companies. These small companies were often started by professors capitalizing on discoveries made in their own academic labs.

Before Boyer and Cohen's invention of recombinant DNA, almost all drugs were small organic molecules synthesized through chemistry or discovered in nature. The 1980 recombinant DNA patent instructs how to splice DNA genes from one species into the DNA of a second species. In the early days of recombinant DNA, the second species was usually *E. coli*, a bacterium that can very quickly reproduce to large cell numbers and be engineered to spit out large amounts of proteins, enabling production of large quantities of human proteins as drugs for commercial sale.

There are many different kinds of protein drugs, for instance hormones such as insulin, monoclonal antibodies for cancer and a host of other diseases, blood factors for anemia and blood clotting, enzymes to cure genetic diseases, cytokines and other immune system stimulators and repressors to fight cancer and treat arthritis. Monoclonal antibody drugs now dominate the list of largest sellers, highlighting the importance of César Milstein's invention. All protein drug types have become subjects of intense discovery and development. Many are on the market. Very few were available until the 1980s, almost none in 1965.

PROTEINS serve not only as drugs but also as targets for small-molecule drugs. How do we find targets for drugs? One answer is from the human genome project. The sequence was completed in 2003 and many of the genes for proteins were quickly identified within it. Many of us thought it would be only a matter of time before we would devise drugs to target the identified disease-related proteins, so that many diseases would soon be cured.

It turned out not to be nearly that simple. An analogy I use for teaching is to compare our state of knowledge then to the New York subway system. Suppose you have a map of the system with all the station stops and frequency of trains. You might say, "I understand the New York subway system. This is all I need to know." But then one afternoon your train doesn't show up at the platform. You now realize you don't know *everything* about the subway system, in fact you know very little. Did your train fail to arrive because it broke down? Because of a power outage? Because the operators are on strike? In order to fix the problem of your train not arriving, you would need to know more about the subway system; and depending on the problem, you might need to know almost everything about the system.

This is where I think we were in 2003 in understanding the molecular basis of disease. The train not arriving is like being ill. And depending on the illness, to cure it you may need to know only a little bit more or you may need to know quite a bit more.

An important consideration is that our proteins interact with each other and with DNA and other molecules in our cells. So if you change or disable a single protein with a drug, you may affect the functioning of several other cellular proteins; that is, a protein might function quite differently depending on the company it keeps. If that sounds as complex as social behavior, it just might be. This behavior could lead to the drug not working at all or to serious side effects. A new field in molecular biology, systems biology, has sprung up to try to understand the many molecular interactions within our body's cells and among cells. This is a very complicated problem, but headway is being made, albeit slowly.

One indication of our incomplete understanding in drug discovery and development is the success rate in clinical trials. From the 1960s through the 1980s, about 20 percent of drugs entering clinical trials reached the marketplace. Today, only 10 percent succeed. How can this be with all the advanced tools of the new biology at our fingertips? We used to think that the new biology would make drug development quicker, more successful, and less expensive.

From my viewpoint as an outside observer of the drug development process, low success rates are caused in part by inefficiencies within big pharmaceutical company operations, perhaps because highly profitable companies have gotten fat and their development staffs have grown too big. As a consequence, too many drugs have been taken into clinical trials, some with little chance of winning approval. Many companies are now reorganizing their operations in an attempt to improve success rates and reduce the cost of drug development.

ANOTHER factor is the FDA's requirement that companies carry out more and more work in clinical trials. Recently it has initiated several "fast track" programs for dire medical needs and for rare diseases to speed drugs through the process. In 2014, there were significantly more FDA drug approvals than in prior years, so success rates may be improving. A further complication is our aging population with patients taking many drugs that may interact adversely.

In an interesting twist, the new biology itself may have reduced success rates by switching from assays on whole cells (so-called phenotypic assays) to ones that employ recombinant-DNA-prepared target proteins isolated from their native cellular environment. While such assays significantly increase the rate and number of drug candidates that may be screened against their disease-related targets, protein interactions within cells cannot be observed, which we now know are important. Although never completely abandoned, phenotypic assays are being reintroduced into the process.

Moreover, the cost of drug discovery and development has soared over the last twenty years. In the 1980s, it cost the big pharmaceutical companies about $170 million to discover a drug and take it through clinical trials to the marketplace. In 2015, some estimates put the cost at over $2 billion, though that figure is disputed by some economists. I have calculated that small biotechnology companies can ferry a drug through trials for perhaps $200 million, ten times less. One of the industry's responses to low success rates and high cost is simply to charge high, sometimes outrageous, prices.

On the business side, a new industry has emerged, known as clinical research organizations (CROs), which conduct trials efficiently for big pharmaceutical companies, as well as for small biotechnology companies with no experience in clinical trials. The concept of using outside companies has also been expanded to discovery research and even manufacturing and sales. This in turn has given rise to the virtual company, where every aspect of discovery and development is carried out by outsiders. The executives in such companies need no labs or employees. They can literally just sit in their office, raise financing, and direct the outside activities. If a drug fails in clinical trials, the company can just be shut down, with no workers to fire, and no facilities or equipment to sell off. The executives are then free to hunt for the next opportunity.

I do not have space enough here to touch on more than a few of the promises of the new biology and only a few of the issues surrounding drug discovery and development, or other areas of biotechnology such as agriculture. The story in these other fields is often similar but there are issues unique to each one, such as GMOs in food agriculture. We have come a long way over the past half-century, and we have a long way yet to go.