

Financing Biotechnology Research: A Firsthand Perspective

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Drawing on my experience with a health care venture capital firm and on much of what I teach at Columbia University's School of Business, I will focus on several practical aspects of the venture capital funding of biotechnology. These include how venture firms that invest in biotechnology operate, how this market evolved, and what areas of biotechnology research hold much promise. I will address these topics from the perspective of Collinson Howe & Lennox (CHL), a Northeast-based venture firm that my partners and I operate.

HOW CHL OPERATES AND HOW THE VC INDUSTRY HAS EVOLVED

In describing how our venture firm operates and how this form of investing has evolved, I will first provide some background on our company as a way to describe the talents that venture firms need from senior management and staff in order to successfully invest in biotechnology.

Some Background on CHL Medical Partners

Our partnership makes early-stage and seed investments in companies operating in the medical sector, defined to include biotechnology, pharmaceuticals, medical devices, and health care services. We are active, hands-on investors who are typically responsible for defining strategy at the companies in which we invest. We often manage these start-ups until we hire a complete management team to run them, and we are often responsible for their financing before they go public. We believe we add value by bringing top financial, scientific, and clinical expertise to bear on managing such ventures (*Table 1*).

Since the emergence of the institutional venture industry in the early 1980s, venture capital firms have generally become more specialized, a trend that char-

Table 1
Collinson Howe & Lennox: Classic Venture Capital

- Seed and early-stage investors
- Using an active hands-on approach
- Responsible for setting strategy, hiring management teams, raising capital
- Bringing to bear top financial, scientific, and clinical expertise
- Well-connected in health care and financial communities

acterizes the nature of the funds that we have managed over the years. In line with most venture capital funds, the ones we have managed are ten-year limited partnerships using capital raised from outside investors. During the 1980s, our activities were widely disbursed amongst leveraged buyouts, specialty retailing, biotechnology, information technology, communications, and just about anything one could imagine. Since then, the world has become a lot more complex and specialization has become necessary in order to identify the best investment opportunities. Our latest fund is called CHL Medical Partners II LP and is \$160 million in size. Over the years, we have been involved in making private investments in about 150 companies, approximately forty of which have been biotechnology firms. Since 1989, we have focused 100 percent of our time on the medical sector.

Some of our portfolio companies might be familiar, including Incyte Genomics, Genetic Systems, Chiroscience, DNA Plant Technology, Procyte, Leukosite, Neurogen, Alexion, and Nova Pharmaceuticals. About 86 percent of our companies historically have completed initial public offerings (IPOs) and been successfully traded (not including the most recent, 1998 vintage, fund). The top one-third of our ventures have generated returns in excess of four times our initial investments; half of those have generated more than ten times, and half of those, more than twenty times.

Our investments with Texas-based companies are Texas Biotech, whose technology came from the Texas Heart Institute, and Gene Medicine (now known as Valentis), built upon research at Baylor University. We also have invested in two Texas start-ups: Odyssey Health Care, which provides home health and hospice care, and SemperCare, which operates long-term, acute-care hospitals.

Senior Management at Health-Oriented Venture Firms

The trend toward sector specialization among venture funds has reinforced the need for venture firms to couple specialized scientific knowledge with the managerial and financial expertise needed to develop a new business. At CHL

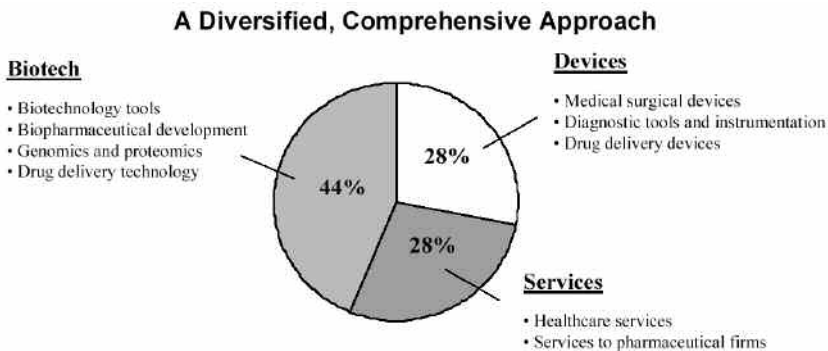
Medical Partners, our technical specialty is medical science. Of the three partners, Ron Lennox, with a Ph.D. in cellular biology and a B.S. degree in molecular biology, has a considerable scientific background, along with an M.B.A. from Wharton. On the financial side, Jeff Collinson has over twenty-five years of experience in private equity investing, along with an M.B.A. from Harvard and a B.A. from Yale; and I have worked in venture capital for about seventeen years, since earning a B.A. and an M.B.A. from Columbia. We are not atypical. Among senior management at venture firms, it is quite common to see a blend of business experience built upon considerable scientific and financial training.

Overall, there are nine people involved with our firm, and there is considerable scientific and business expertise among our future partners as well. For example, Greg Weinhoff is an M.D. who has an M.B.A. from Harvard, and Goga Vukmirovic, our latest addition, majored in molecular biology at Princeton, where she wrote a senior thesis on a topic in functional genomics. Looking through our firm, one sees a great depth of venture capital and medical-oriented experience.

Specialization, Diversification, and Sector Selection

At CHL Medical Partners, we try to balance the gains from specialization with the need to diversify across medical solutions. Although approximately half our business is biotechnology, our strategy is to diversify across the health care marketplace because we believe the solutions to medical problems could arise not only from biotechnology but also from medical devices and services concepts. Within biotechnology, we have invested in biotechnology tools, biopharmaceutical development, genomics, proteomics, and drug delivery technology (*Figure 1*).

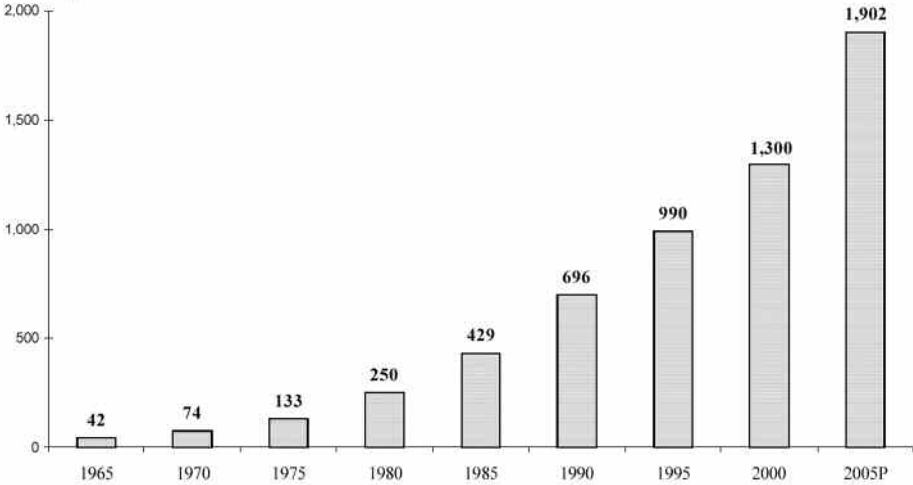
Figure 1
Collinson Howe & Lennox: Sector Analysis



The solutions to medical problems may come from any or all segments.

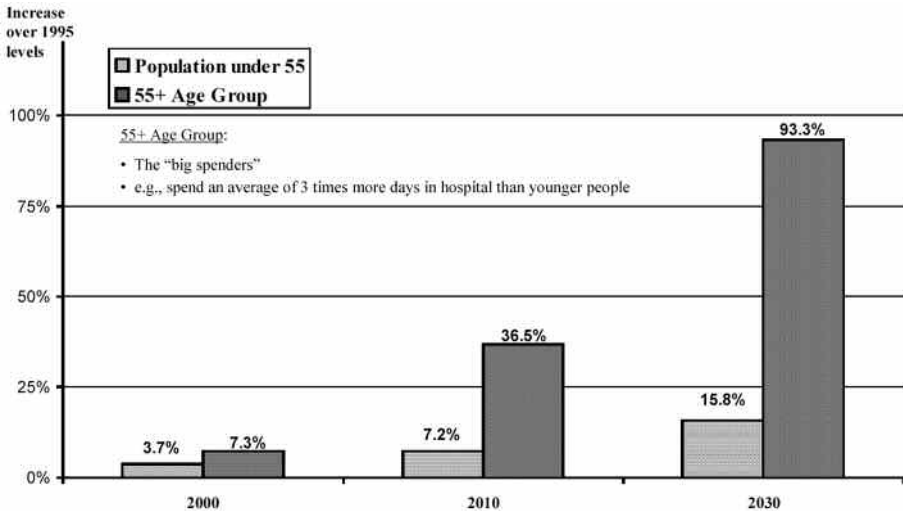
Figure 2
U.S. Health Care Expenditures

Billions of Dollars



SOURCE: Centers for Medicare & Medicaid Services, Office of the Actuary.

Figure 3
The Aging of the Population: The Baby Boomers Move Through



SOURCE: U.S. Administration on Aging.

Investing in health care is attractive to us because health care expenditures have grown to become a large part of the U.S. economy, amounting to nearly 15 percent of GDP. Figure 2 depicts U.S. health care spending in billions of dollars over five-year increments.

Most of these expenditures are service-oriented, with only 10 to 12 percent spent on pharmaceuticals. The primary reason health care expenditures are growing at an increasing pace is the aging of the population, portrayed in Figure 3. The right-hand bars depict the percentage increase in the population that is over age 55 relative to the 1995 levels, while the left-hand bars depict population growth of those under age 55. This figure shows that the over-55 age population segment, which accounts for most medical spending, is growing about five times the pace of the rest of the population. This is a fundamental force that is propelling growth in health care spending. Moreover, with better development of drugs, this increased demand could be accommodated with much less expense to the system.

We see the opportunities in biotechnology as building off of advances in molecular biology, genomics, and proteomics, listed in Table 2. Currently, all the drugs on the market act on a total of about 500 targets, but there are upwards of 35,000 genes in the human genome, and many new targets for drug therapy remain to be identified. What we are really trying to do as investors is get a little bit closer to the ultimate goal of personalized medicine. More specifically, the goal is to really understand the genetic basis of disease and how an individual's genetic makeup influences the effectiveness of drug therapies. Such advances would hopefully lead to better, more specific therapies with fewer side effects.

Table 2
Human Genome Opportunities

<ul style="list-style-type: none"> • All the drugs on the market today act on a total of about 500 targets. • There are around 35,000 genes in the human genome. • Many new targets for drug therapy remain to be identified. 	
<p>The genetic code is not the end point but the beginning of a new phase in medicine. <i>(Money, September 2000)</i></p>	<p>In the long run, genomics and proteomics will probably transform the pharmaceutical business, helping drug makers to develop better drugs faster and with fewer side effects. <i>(Economist, Feb. 17, 2001)</i></p>
<ul style="list-style-type: none"> • Understanding the genetic basis for disease and how an individual's genetic makeup affects drug metabolism and toxicity will lead to better, more specific therapies. 	

The Role of Universities in Biotechnology Ventures

The critical role of science in the biotechnology arena naturally leads us to work closely with universities. With our headquarters in Stamford, Conn., Yale University is a natural partner. As Table 3 shows, we have worked closely with the Yale technology transfer office to establish and fund seven start-up companies.

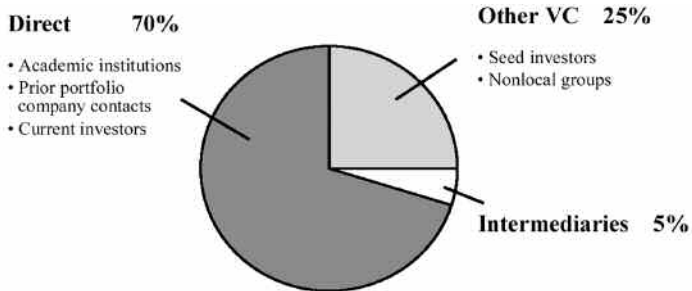
Mirroring the experience of other medical-oriented venture funds, we have seen a shift in how the returns from joint ventures are shared with universities. While Yale-based technologies and expertise led to the creation of two of our biotechnology companies in the early '90s, Alexion and Neurogen, the financial returns to Yale consisted mostly of licensing fees for their technologies as opposed to equity ownership, which was typical of the environment at the time. Both of these companies became public, and depending on how their stock prices have traded, their market values have ranged anywhere from \$150 million to over a billion dollars. Recently, in contrast to these initial ventures, our last five venture deals with Yale, made between 1998 and 2002, involved companies founded with the technology transfer office at Yale, whereby Yale University received an equity stake in exchange for licenses to technologies invented at Yale. So while it is still too early for these companies to consider initial public offerings, we are hopeful those days will come and Yale's returns, though riskier, could be substantially greater than had they just taken licensing fees. This exemplifies an important emerging trend of ventures involving tech-

Table 3

CHL Medical Partners: The Yale Relationship

<ul style="list-style-type: none"> • Numerous Companies Neurogen Corp. Inc. (1988) Founding investor; active director Alexion Pharmaceuticals Inc. (1994) Early investor; active director polyGenomics Inc. (1998) Founding investor; active director Molecular Staging Inc. (1998) Founding investor; active director Cellular Genomics Inc. (1998) Founding investor; active director Protometrix Inc. (2001) Founding investor; active director VaxInnate Inc. (2002) Founding investor; active director • "Active" means we strive to create value through management recruitment, financing, identification of corporate partners and negotiation of collaborations, incensing key technology from elsewhere; strategic guidance aimed at commercialization and long-term value creation.

Figure 4
CHL Medical Partners: Portfolio Analysis, Deal Sources



nology transfers from universities, and Yale has emerged as one of the leaders in making this transition. Nevertheless, many other institutions remain reluctant to take equity and continue to prefer royalties.

There are other benefits to universities from venture deals. For example, we tend to situate the companies we fund from Yale around New Haven in order to benefit from the local talent pool, and Yale has been very pleased about bringing new companies and all the employment they help generate to the city of New Haven. From just our last five equity-share ventures alone, over \$100 million of capital has been brought into the region thus far, and close to 100 new jobs were created, contributing both to the university's bottom line and to local development.

I would like to point out that most of our deals come directly from inventors, academic institutions, or from people in successful, earlier ventures. From Figure 4, one can see how few opportunities we have generated through intermediaries. It is important for us that the source of technology makes contact directly with us.

WHERE ARE THE FUTURE OPPORTUNITIES FOR BIOTECH VENTURE FIRMS?

Later, I will discuss the particular opportunity facing venture capitalists in the area of proteomics; however, first I'd like to provide the following introduction to how we develop biotech venture opportunities. Broadly speaking, we have found that important venture investment opportunities continue to emerge when one considers the vertically integrated pharmaceutical industry from the perspective of the potential of developing large horizontal players.

Drawing on the transformation of the computer industry illuminated by Andy Grove in his 1996 book *Only the Paranoid Survive*, where he describes

how the computer industry transformed itself from being vertically integrated to being dominated by horizontal players, we see some parallels in the pharmaceutical industry. Figure 5 illustrates the vertically integrated pharmaceutical industry on the left-hand side, with the activities broken down into five categories: sales and distribution, manufacturing, clinical research, compound discovery and development, and research/target discovery.

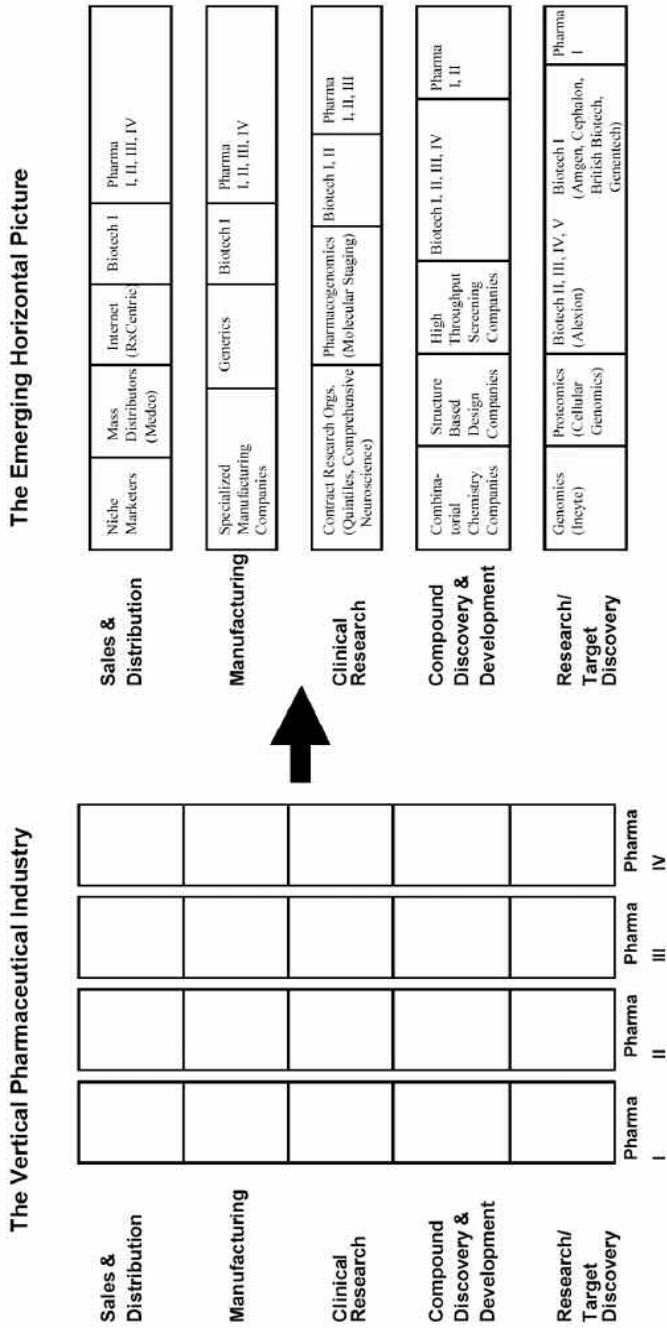
Historically, large pharma houses have been justifiably proud of their own research and target discovery capabilities, which they housed internally. Prior to the advent of combinatorial chemistry technologies, the pharmaceutical companies could also be very proud of their own proprietary compound libraries. Many big pharmaceutical firms continue to house their own clinical research, to manufacture all of their own pills, and to maintain huge sales and distribution forces. Recently, however, a number of venture-backed companies have emerged as potentially significant horizontal players that are transforming the way pharmaceuticals are discovered, developed, and brought to market.

For example, we founded Incyte Genomics to serve as a source for much of the research and target discovery for the pharmaceutical industry. Specifically, Incyte Genomics focused on sequencing the human and other species' genomes and providing access to its database to pharmaceutical industry clients who pay sizeable annual subscription fees under multiyear contracts. Currently, most of the top pharmaceutical companies subscribe to Incyte's databases. In addition to subscription fees, Incyte Genomics is also entitled to royalty payments on discoveries made using the databases that eventually get developed and sold in the marketplace. We believe that a company such as Incyte has the ability to dominate a horizontal segment of the pharmaceutical industry, much as Intel did within the chip sector of the computer industry.

Similarly, combinatorial chemistry, structure-based design technologies, and high-throughput screening tools are enabling more efficient compound development, and companies that have these technical capabilities have the potential to become horizontal leaders and integral parts of the industry's drug discovery and development process. Outsourcing clinical research to clinical research organizations has already become commonplace, but we expect many additional opportunities to arise with the emergence of pharmacogenomics and advances toward personalized medicine.

Within the sales segment, we have yet to see an outsider or newcomer grow into gaining a dominant position. Nevertheless, Medco Containment (prior to its acquisition by Merck) opened up a significant position as a mass distributor of drugs. We believe that the Internet could fuel further change by giving doctors easier access to drug information and pharmaceutical firms. In particular, we can conceive of lowering the cost of selling drugs by enabling pharmaceutical firms to introduce therapies to physicians at the physicians' own convenience over the Internet. Those companies that can provide these efficient systems for

Figure 5
The Horizontal View



pharmaceutical firms to reach physicians may become significant companies; hence we have invested in RxCentric.

Opportunities Posed by Advances in Proteomics

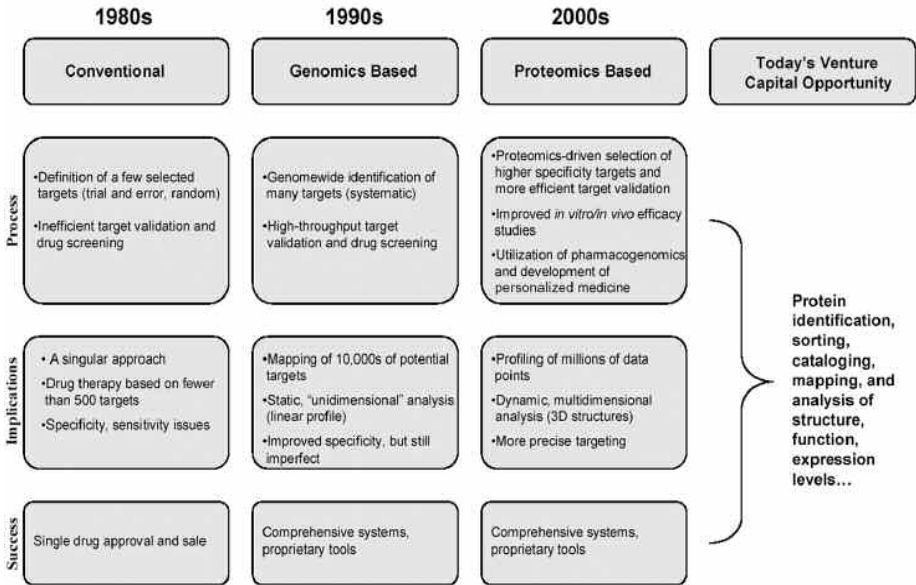
We see the coming proteomics era as potentially presenting a number of exciting venture opportunities. Over the past decade, the sequencing of human and model organism genomes has resulted in an enormous proliferation of information, transforming biology from a data-poor to a data-rich science. Historically, to understand the form and function of organisms, scientists have had to increasingly define more narrowly the unit of study. Looking at the entire animal gave way to a focus on increasingly smaller parts—from organs, to cells, to molecules. The reductionist approach of dissecting the whole into its constituent parts and studying each part independently has dominated the field of molecular biology over the past century; with the discovery of the structure of DNA, the unit and focus of study became the molecule. This approach has been a powerful strategy that will continue to have a role in scientific research. Yet today, with the genome sequencing efforts for humans and numerous model organisms nearly complete, there has been a shift away from the reductionist approach in research in favor of genomewide, context dependent, global analysis. The promise of genomics and proteomics has been fueled by the promise of holistic, whole-genome- and proteome-based approaches that generate and integrate sequence data, expression profiles, protein interaction maps, and protein structural and functional information.

Significant opportunities for venture capital investors exist in funding the development of technologies to understand and exploit this flood of information and data, and proteomics in particular has the potential to enhance pharmaceutical productivity and tremendously impact the drug discovery and development process.

Over the last twenty years, our biotechnology investing practice has changed as the focus of and the technology involved in drug R&D process changed (*Figure 6*). In the 1980s, a single drug target or a drug that was pretty interesting could be developed and sold at a significant profit, provided it was an important therapy. Fundamentally, success was defined by a bottom line driven by a single drug approval and sale.

In the 1990s, our investments shifted more into genomics-based research, where the success of a venture was based on the development of comprehensive systems and proprietary tools that enabled pharmaceutical companies to utilize the massive amount of information coming from the genome-sequencing projects. The overabundance of raw information, and lack of adequate tools to interpret and leverage it into marketable products, became the bottleneck in drug development. Hence our companies were designed to provide the tools

Figure 6
The Transformation of the Drug R&D Process



that mine the genome sequence information and generate a wealth of novel therapeutic targets. Genomics offered pharmaceutical firms a promise to decrease time to drug development, increase the success rate in clinical trials, and lower R&D costs. As investors, we were now taking pure technology risks rather than drug development risks. This was an important feature of the genomics era ushered in during the 1990s. Enormous investment returns were available for those who developed the successful proprietary genomic tools and systems and sold them effectively to the pharmaceutical industry.

Yet many of the early promises of genomics (such as decreased time to drug development, increased success rate in clinical trials, and lower R&D costs) have not materialized. It has become clear that medical breakthroughs do not follow from the genome sequence information itself. Rather, the breakthroughs will come from focusing on understanding the function and relationships among gene products (i.e., proteins) in a changing environment. Going from knowing the coding sequence to understanding the protein function is not a trivial task. Identifying any sequence feature is not necessarily indicative of its function, and the function of a particular gene product is highly context dependent and is rarely unique, as there are numerous instances where there is a "backup" system (i.e., redundancies in signaling pathways) in place that can compensate for

a particular loss of function. Dynamic, multidimensional analysis is needed to understand the structure and function of proteins, as particular proteins can be present in varying amounts at different times and in different locations within a cell. While the identification, sorting, cataloging, and analysis of structures and functions of proteins will be more important and difficult to undertake than was the case with genomics, leveraging proteomic information could alleviate many bottlenecks in drug discovery and development and potentially enhance pharmaceutical productivity.

Investing in technological tools continues to present attractive investment opportunities because researchers need increasingly more complex and sensitive technologies to carry out proteomic analysis, and the data management requirements alone supercede those of genomics by at least four- to fivefold. The tools market is attractive because it is unregulated (no FDA approvals necessary), businesses can scale quickly, and products are patent protected. Moreover, for investors, exit alternatives are wide ranging. There has been substantial M&A activity by large, publicly traded tool companies seeking new technologies to complement their existing portfolios, and numerous pharmaceutical and biotechnology companies seeking technologies that complement and extend their R&D efforts, offering them unique, proprietary techniques for drug development.

Genomics and proteomics have brought about a revolution in the field of biology and have the potential to fundamentally transform the pharmaceutical industry. Increasingly, diseases will be diagnosed and treated based on a greater understanding of both the disease pathology and the mechanism of particular drug action, further integrating drug discovery with disease characterization and diagnosis. With advances in proteomics, we are many steps closer to fulfilling the promise of personalized medicine to offer more effective and less toxic therapies to individuals. But even before personalized medicine becomes a reality, opportunities abound for creating significant value by developing enabling technologies and utilizing them in drug discovery and development.