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The Rise of Advanced Biotechnology in the Age of Genomics

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What's Evolving on the Innovation Frontier:

The Rise of Advanced Biotechnology in the Age of Genomics

No industry better illustrates the idea of the innovation frontier and the impact of the expansion of scientific knowledge and its driving influence on the evolution of technology than biotechnology. In 1973, Herbert Boyer and Stanley Cohen (at UCSF and Stanford University, respectively) invented the basic genetic engineering techniques enabling the creation of recombinant biotech therapies such as insulin. Since then, the biotech industry has seen tremendous progress on many fronts, with a series of breakthroughs in the treatment of various diseases, some of which we touch on below.

The birth of this knowledge-based industry demonstrates how the evolution of core technologies can spawn new industries. From just a collection of techniques and tools in the 1970s, the biotech industry has developed into a global industry with annual worldwide sales of $150 billion and growing. The innovative potential of this industry remains as robust as ever, especially with the introduction of new biotechnologies, such as genomics and gene therapy. Here, we touch first on the history of the industry and then shift to a discussion of a few of the newer technologies creating growth and investment opportunity.

A Thumbnail Sketch of the History of Biotechnology

The process for the creation of important new technologies, such as biotech, typically starts with important new theories and principles developed within academia on the knowledge frontier, which is always progressing ahead of its practical application on the innovation frontier. From new scientific knowledge to its commercial application, it is typical for a very long gestation period to play out, often taking as long as 10-20 years to move from theory to technical feasibility and on to economic feasibility. For example, it took nine years from the invention of recombinant engineering to FDA approval of recombinant insulin, the first major biotech treatment to be approved, in 1982.

"Overnight successes" rarely happen overnight. They usually experience a long process built on the steady and progressive evolution over decades of a core set of technologies. One could argue that biotechnology—using biological-based techniques and medications to treat disease—goes back further in time than the Boyer/Cohen breakthrough mentioned earlier.

Most fundamental was the evolution of the microscope in the 1660s-1670s, which over time enabled and led to the development of the germ theory of disease (that microorganisms, such as bacteria and viruses, are the cause of many diseases). It took over 200 years until Louis Pasteur developed the pasteurization process in 1865 to kill bacteria in beer, wine, and milk, around the same time that Joseph Lister developed antiseptic surgery, with the sterilization of surgical instruments and the treatment of wounds to prevent infection. These key developments are what led ultimately to the invention of modern vaccines, marking the first step toward what we would today call biotechnology.

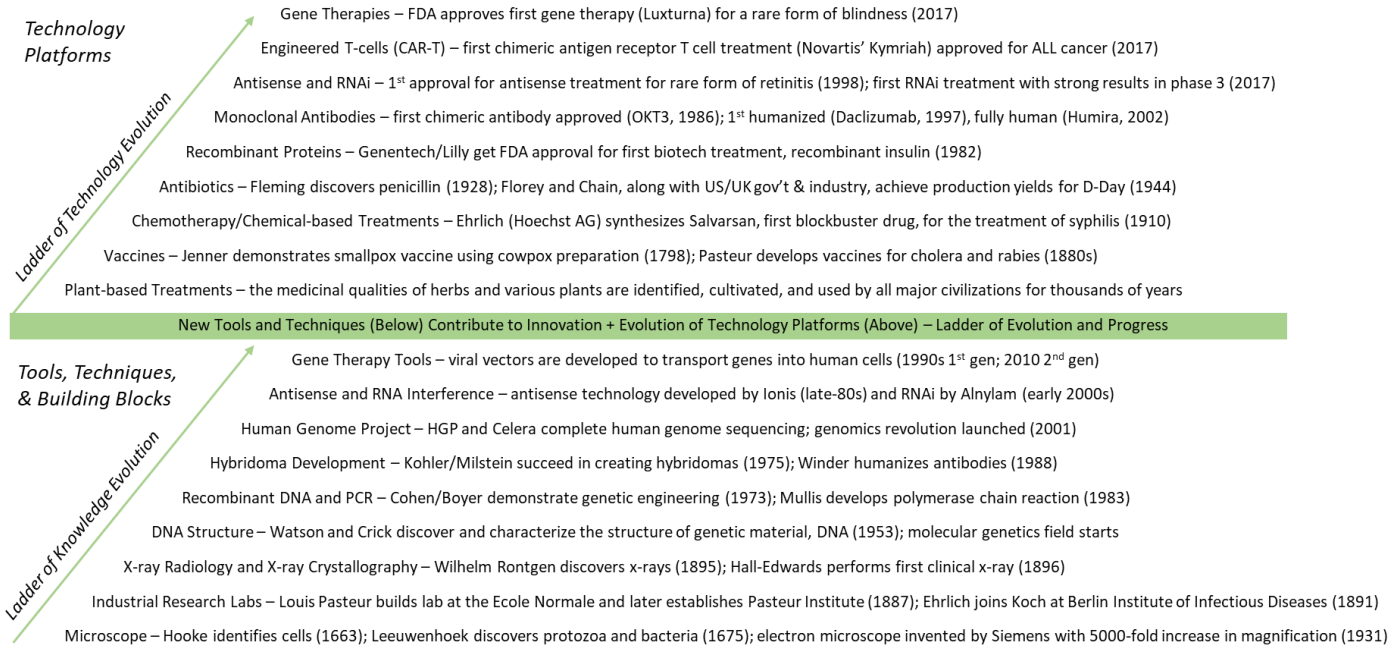
The theoretical foundation of vaccines took well over a century to develop into effective and reasonably consistent medicines. The story begins with Dr. Edward Jenner, who demonstrated the principle of a smallpox vaccine using a cowpox preparation in 1798. It took nearly a century, well into the 1880s, for Pasteur to build on this knowledge by creating a professional research lab-based process for creating

vaccines, including vaccines for cholera and rabies. Hospital and institute-funded research led to further new knowledge, with Alexander Fleming's 1928 discovery of the antibiotic qualities of penicillin. It took other scientists, notably Howard Florey and Ernst Chain, along with the US and UK governments and industry, to scale up penicillin in time for the D-Day invasion in 1944. These developments sparked the creation of the antibiotic industry, which, in turn, laid the foundation for the modern pharmaceutical industry.

The next decade witnessed the decoding of the mystery of DNA. In 1953, James Watson and Francis Crick characterized the structure of DNA, and, with others, unraveled the central dogma of DNA, that genes are transcribed into messenger RNA, which are then translated into proteins, the workhorses of cellular processes. The major consequence of this discovery was to lay out the initial evolutionary path of innovation toward manipulating these processes at the molecular level and, ultimately, creating genetic engineering.

See the diagram below for an overview of the evolution of biopharma technologies. The bottom half of the diagram shows the progressive development of various important enabling tools, techniques, and building blocks. These enabling technologies, along with many other techniques, are what led to the evolution of a growing number of technology or innovation platforms and products, shown in the top half of the diagram. Think of it as two ladders, the ladder of knowledge that leads to the ladder of technology evolution. The pharma/biotech industry is one example of how this process works.

Evolution of Tools and Technology Platforms for Pharma/Biotechnology



The biotech industry has evolved over the 35 years from the approval of insulin in 1982 to now, from applying early tools to create replacement recombinant proteins (such as insulin for diabetics) to more advanced technologies, including monoclonal antibodies with molecular targeting capability (for example, fighting cancer) and, more recently, gene therapy for potentially curing genetic diseases.

The Biotech Innovation Frontier

Each of these technologies progressed through an evolutionary path that led to improved performance (better efficacy and safety in treating patients), and, in the process spawned a very large, global growth industry. This created significant investment opportunity. Today, we see this process continuing and even broadening to address a wider diversity of diseases. Biotechnology continues to evolve, and thus will remain a leading growth industry for many years to come. On biotech's innovation frontier, there is important progress in three areas: 1) antibody engineering, 2) RNA targeting, and 3) gene and cell therapy. We will touch on each of these key technologies below.

The Evolution of Monoclonal Antibodies

Basic recombinant or replacement proteins were the first major biotechnology to be commercialized in the 1980s and 1990s, but it was the second major biotechnology, monoclonal antibodies, that generated the next wave of growth in the late 1990s, and drives sustained growth still today. From less than $5 billion in sales for antibody-based therapeutics in the late 1990s to over $100 billion in global sales currently, this example demonstrates the power of innovation to create a growth industry.

Without getting too technical, monoclonal antibodies harness the power of our immune system to create antibodies that can be highly targeted for specific diseases. Examples include monoclonal antibody drugs for treating breast cancer (Herceptin) or rheumatoid arthritis (Humira). Antibody biotechnology went through a clear evolutionary process across four major generations, from murine (mouse-based antibodies) to chimeric (part mouse/human), on to humanized and fully human antibodies (mostly/all human antibodies). As the technology evolved from murine and chimeric to humanized or fully human, the technology saw improved efficacy and reduced side effects.[1]

Most monoclonal antibodies in clinical trials today are either humanized or fully human, but the technology has not stopped evolving. In fact, there is a growing array of new engineered antibodies, from bi-specific antibodies (that can address two different targets versus only one for traditional antibodies) to nanobodies (smaller antibodies with unique properties). We believe that these next-generation antibodies will lead to improved treatments and large new market opportunities, in turn creating new sustainable growth investment opportunities.

RNA-based Gene Targeting Comes of Age

The ability to address disease at the genetic level—at the level of genes and gene expression—has been exceptionally difficult, despite its high potential for addressing both monogenic (single gene) and polygenic (multiple gene) diseases. However, the knowledge frontier has moved forward rapidly of late, contributing a variety of new tools and techniques to create not only technical but therapeutic feasibility for modulating genes and gene expression. Two technologies, in particular, are now generating strong clinical results modulating genes: 1) antisense technology and 2) RNA interference (RNAi) technology. Both antisense and RNAi are nucleic-acid based treatments that target the RNA part of the central dogma of genes we discussed above. Both technologies have the power to downregulate or modulate the gene expression of functional proteins. This power to tune gene expression is of profound importance, and future generations of these technologies may address a growing array of diseases.

Both technologies have evolved through successive generations to arrive at a point where their clinical utility is now ready for mainstream adoption. Early antisense treatments were either degraded too

quickly in the body, or they required doses that generated unacceptable toxicity. Now, with next-generation chemical modifications, antisense treatments are more effective and becoming less toxic. The approval of Spinraza for the treatment of spinal muscular atrophy demonstrates that antisense has crossed an important threshold for utility in treating disease, particularly neurological and rare disease. In the article, "ASO Therapy: Hope for Genetic Neurological Diseases," published in the *JAMA* medical journal, clinical neurologist Stefan Pulst, MD, at the University of Utah states, "One thing that drew me to ASO [antisense] therapies was that, having a gene defect in hand, ASO has offered the opportunity to directly target the primary cause of the disease, and I think that's very attractive."[2]

RNAi technology is also on the threshold for commercial utility, as this technology has now shown very strong clinical results for TTR amyloidosis, another rare disease. The application of these treatments will likely broaden in the next 5-10 years, demonstrating ongoing important innovation in the biotech industry.

Gene and Cell Therapy Finally Break Through Key Hurdles

Gene therapy was theorized as a potential treatment for genetic diseases not long after DNA was characterized, but its development has been a difficult and tortuous one, marked by what initially appeared to be insurmountable hurdles. The idea of replacing faulty genes with functional genes in patient cells seems straightforward, until faced with the daunting reality of how to actually get genes into specific cells—and do this without causing genetic damage, inflammation, or inducing cancer. These hurdles seemed to throw a roadblock in the development of gene therapy when a patient died in 1999 during a clinical trial for a gene therapy at the University of Pennsylvania. The patient developed a strong immune reaction to the viral vector that was used to transport the genes into cells.

The newer breakthroughs for gene therapy have been multifactorial, but the critical ones were the development of next-generation viral vectors to deliver therapeutic genes, and the choice of which diseases and cells to target.[3] For example, clinical data has shown remarkable efficacy and safety for newer gene therapies targeting hemophilia A. Next-gen gene therapies are also being developed for sickle cell disease, as well as a growing number of other genetic diseases.

Another breakthrough has been the development of CAR-T therapies for the treatment of hematological cancer (such as leukemia and lymphoma). By genetically engineering T cells to target cancer, these treatments can train the immune system to eradicate certain types of cancer.[4] FDA approval of Kymriah for acute lymphocytic leukemia (ALL) in 2017 demonstrates the utility of this unique cell therapy.

Genomics Enhances the Power of Biotechnology

Lastly, another fundamental technology that contributes to biotech innovation is genomic sequencing. The Human Genome Project and a competing project by Celera fully sequenced the human genome by 2001. Now, with the cost of sequencing moving below $1000 per genome, genetic research is experiencing a renaissance, leading to new knowledge about the genetic and molecular causes of many diseases.

A recent statistic showed that molecular and genetic data can also improve the probability of success for approval of new treatments. Data from a study by the Biotechnology Innovation Organization (BIO) showed that clinical trials that use biomarkers or molecular targets can improve the probability of clinical trial success from 8.4% (without biomarkers) to 25.9% when taking a new drug from Phase 1 to

FDA approval.[5] Genetic research also generates numerous new disease targets that biotech companies can address with new monoclonal antibody, antisense, RNAi, or gene/cell therapy-based treatments, and, in turn, sustain industry growth for many years to come.

While the biotechnology industry has come a long way in treating many diseases, there is substantial room for new innovation that treats many more diseases with unmet needs. This will fuel sustainable growth for biotech over the long term.

Sources:

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