The Convergence of Disruptive Technologies Enabling a New Industrial Approach to Health Products

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I have prepared this talk to cover two areas. First, I want to present a convergence of disruptive technologies that are driving new therapeutics. I will then finish with the situation in the state of Texas with regard to the traction we have in biotechnology, the companies being created, and what strength our academic community is providing to stimulate the initiative.

Bear with me for a moment while I create a yachting analogy for the biotech industry. The Vendee custom yacht is a single-person-managed yacht with a maximum speed of about 35 knots and the capacity to go nonstop around the world. In the Vendee race, it goes south, following a southern arch. This is the same arch undertaken at the turn of the century by Shackleton, who needed twenty-four months and a substantial crew.

The difference between the experiences early in the century and the experiences with the Vendee Great South Yacht Race is the difference in technologies, which enables a single individual to achieve the objective. My message is that technology empowers. It is the focus on new technology by biotechs that allows them to sail faster than large pharmaceutical firms.

The Vendee race also has some good analogies to business. Let me illustrate. Four yachts were sunk. Three were sunk under conditions in which they had full appreciation of conditions and their position. The fourth yacht knew where it was but not the surrounding conditions. It had lost its technology and thus was unable to estimate the surrounding conditions.

There were two categories of rescuers for these failing yachts. There was the individual, high-tech rescuer, as illustrated by Peter Gross, who found the failing boat in the vast southern ocean. He utilized GPS technology and had full knowledge of the conditions surrounding both single-man boats. In the second

example, the rescuer was disadvantaged because she lacked GPS position and knowledge of the surrounding environment. The third situation utilized a large interdisciplinary team. All came to the rescue of individual entrepreneurs and, in this case, individual sailors. The outcome of the race was one lost at sea, one racer-to-racer rescue (I equate that to biotech-to-biotech rescue), and two rescued by large organizations (I equate that to pharma). The overall outcome of the Great Southern Race: one winner, eight finished, four sunk, three rescued, and one lost. That is about the same outcome on biotechnology investment. I hope you remember this illustration as an example of what it takes for high tech to succeed.

I will now shift from this introductory illustration to discuss the technologies that are enabling or empowering smaller numbers of scientists to do more. HIV drugs have been discussed. It was my great pleasure to be senior vice president at Merck as we developed the reverse transcriptase inhibitors and proteinase inhibitors. I cannot recall a time in science that has been so rewarding. We were able to see these drugs safely introduced and death rates fall. It was an exciting, exciting time. We focused on the technologies necessary to achieve that objective in eight and a half years, which was a record time for drug approval by the FDA. No other drug development effort has ever matched that effort. It started with the isolation of the HIV virus, isolation recombinant DNA technology, cloning, sequencing, and understanding the structure and function of the HIV virus. Converging disruptive technologies were fundamental to the project; without them we would have had no product.

Never underestimate the power of cell biology. Those who criticize the Nixon era war on cancer, saying it achieved little, were wrong. The war on cancer gave the United States dominance in the area of cell biology. It was the ability to grow cells and use a virus's DNA to infect a cell that allowed us to satisfy Koch's postulates that the killing of a cell was caused by a virus. Then came the ability to study drug targets by genomic sequencing and predicting gene function and thus matching the cell biology to drug development.

We had lucky breaks in the first two HIV drugs. There were cancer products in development that were structurally similar to the inhibitors of the reverse transcriptase and the antihypertensive drugs. We were off and running, as were many other pharmaceutical companies. We were on target within a short period of time. Thus by recombinant DNA technology, Koch's hypothesis was satisfied by cell biology, followed by the lucky break of having the lead compounds. We are now developing new products (integrase inhibitors and CCR5 and 4 blockers). But this development is more difficult because we lack leads; thus we have to find them by combinatorial chemistry, leading to a longer development time.

Let me shift to replacement inhibitory proteins. Examples of replacement proteins would be Epos Factor 8, interferon, growth hormone, and insulin. Examples of the inhibitory proteins would be monoclonal antibodies now used

for anticoagulation, arthritis, and cancer. There are some very novel new protein products that I would put under the classification of a Trojan horse. It looks pretty friendly, but if you let it in the door to that receptor, it kills the receptor's function. Examples include emerging drugs for arthritis and cancer. These are true recombinant molecules that create a new event at the target receptor. Recombinant DNA technology and bioinformatics were used to predict functionality of these proteins and thus select them for drug development. We drew upon an accumulation of data from huge databases and bioinformatics that were critical to the identification of proteins and their corresponding monoclonal antibodies. If you examine the products from this arena, many of them are fashioned to a native molecule. We can, however, improve on nature for pharmaceutical products. We can make it an injectable, achieve a therapy peak, make a longer action, and add a safety factor. The study of proteins and monoclonal antibodies opened a new therapeutic area and created biotechnology.

Let me shift to HIV vaccines. Utilizing DNA technology, viral genome sequencing as well as delivery of viral vector constrictions, HIV vaccine strategy is directed at making a harmless virus that delivers the immunological challenge and creates the immune response protective from HIV. Such a safe virus was made possible by our understanding its genes and predicting what could be removed from these vectors to create the vaccine. Cell growth and cell transfer were critical to success.

HIV vaccines have been extremely difficult to develop. We had a poor understanding of how to protect against HIV infections. We had to discover the process by which the virus made cell entry, permanently established itself, avoided the immune protective system, and others. The creativity of individual scientists to understand this biology has made possible the new vaccines now in trial. There have been misjudgments made along the way. We know now that antibodies alone do not work to protect individuals. What worked for hepatitis B, human papillomavirus, and other viruses did not work for HIV. The entire strategy had to be changed to accommodate so-called viral cell killing. Last week we witnessed the first failure of this strategy that used a canary pox virus vaccine. Even with knowledge and good design, we still have a challenge on the use of these disruptive tools to achieve a vaccine. One trial I want you to follow now is one using a combination of a DNA-injectable, followed by a protected artificial virus construct for T-cell immune stimulation. It has protective effects for the primate with HIV. Such a vaccine may protect individuals from infection by clearing infected patients of their residual infected cells, those not eliminated by drug cocktails.

Next, I will focus on Alzheimer's. Consider where we were with Alzheimer's drug development ten years ago. Our efforts have been absolutely focused and put into logic by the discovery of disease genes responsible for inherited forms of Alzheimer's. The study of human genetics and the discovery of the disease–

gene associations set the field to work in a logical manner. Before these discoveries we had no conceptualization of the disease or logic for drug development. There are many more opportunities from human genetics. Humans have about 5,000 to 6,000 inheritable diseases whose causative genes are yet to be discovered. The disease–gene relationship represents the starting point for conceptualizing the disease process and removes the biologic chaos. Approximately forty disease–gene associations are being discovered per month. Ten years ago it was ten per year. This accelerated discovery rate can be connected to the scientific empowerment of the human genome project completed in 2003.

High-throughput drug screening and combinatorial chemistry have accelerated the discovery of lead compounds. In the past, pharmaceutical companies amassed vast collections of chemical compounds, without a strategy to move from one compound to others efficiently. All changed with the conceptualization and implementation of combinatorial chemistry, where one could begin to build platforms of space-occupying chemistry. This created large numbers of compounds. Now, a million-compound collection is not uncommon. Furthermore, rarely do the first compounds have the best properties. Medicinal compounds are modified for safety, drug distribution, dosage, etc. Combinatorial chemistry has that strategy to achieve such objectives. Scientists can move rapidly. A single scientist can develop from a single lead compound a new set of 100 or 500 related compounds within a week. Such productivity previously required teams of 100 to 500 chemists. Without high-throughput drug screening and computer analysis of large numbers of compounds, none of this would have been achieved. Each company now has adapted this integrated technology for drug development. Alzheimer drug development makes tremendous use of combinatorial chemistry, high-throughput screening, and human genetic gene leads to achieve the objective of new drugs.

The most important development involving descriptive technologies is that of disease models and the development of designer species. It makes use of genome sequences, human genetics, mouse genome sequences, and stem cells. We have known about the stem cell for over twenty years. It is the cell that can be manipulated to realize all the mouse models that we constructed over the past twenty years. Stem cells have been very much in the research forefront and are used very proactively. We are in the early stage of use of stem cells for human disease.

Let me illustrate a stem cell utility. Let us assume there are five genes involved in Alzheimer's. We know that for a single patient with Alzheimer's, we can identify one of four genes. By transfer of the patient's cell nucleus into a laboratory-friendly cell type, we would have the capacity to test a single drug for efficacy. This provides a preclinical test for therapy response and drug choice.

Let's focus on the creation of mouse disease models. Companies like Lexicon Genetics, located in The Woodlands, Texas, and several others have carried out gene knockouts in the mouse to create disease models, allowing a scientist to

examine a single gene and determine the disease. The hospitalization and examination rate of these mouse knockouts is a thousand per year. Thus Lexicon has industrialized disease–gene discovery for mice and man and accelerated drug development.

Let us now focus on Texas. Texas is a big agricultural state. Our northern neighbor, Canada, is also a large agricultural entity. Canada committed substantial resources to developing special species of advantage in fish, forest, commercial crops, and production animals. I use this as an example of how the empowering technology in genome science allows you to reach not only from the mammal but also into very important commercial species. We need to accelerate our Texas initiatives in biotechnology.

What has been achieved by biotechnology? Of the new therapeutics, 35 percent comes from innovative products being developed out of biotech corporations. That is a very aggressive pipeline of new therapeutics. We have numerous examples of biotech products being licensed and acquired by large pharma. The point to be made: Biotech can move faster and more focused than pharma. Big pharma is that locomotive preparing to have the switches thrown. Big pharma is powerful in development; biotechs are weak in development. Biotechs can prove the principle of the therapy, bring the product to the point of high likelihood of utility, but need big pharma to engage in development. Rarely can a biotech go to FDA approval with available funding.

What are the novel products coming out of biotechnology? I can assure you that few large pharmas would have taken on the uncertainty of these new therapeutics. They just will not take the challenge; there is too high a risk. There are many biotechs. Some will succeed. Some will fail. It is, however, biotechnology that will discover an important pathway for regulating cancer, controlling cancer, regulating diseases like type 1 diabetes, multiple sclerosis, and others—all based on cytotoxic T lymphocytes (CTLs).

There is not one pharma that would have touched antisense because of its novelty. The first ophthalmologic products are now in use. Isis Innovation started antisense therapy. Almost all vaccines are licensed from outside biotechs. Biotechs now lead the development of terrorism vaccines. No pharma would approach gene therapy—again based on risk. Wonderful opportunities now exist for organ and cell transplantation, and these will rely upon biotechs for advancement.

Let's examine the financial drivers for biotechnology in Texas. As shown in Table 1, the National Institutes of Health is the gorilla. The National Science Foundation is increasing in importance. Pharma exceeds these two because of the high cost of development. Venture capital, while small, is a key stimulator. State contributions are about a million nationally.

Diversification and building high-tech industry are critical to the state. Let's examine the fuel for the discovery engine in Texas (*Table 2*). Listed here are

Table 1
Financial Drivers of Biotechnology in Texas

National Institutes of Health	$23.0 million
National Science Foundation	$ 4.8 million
Pharmas	$26.0 million
Venture Capital	$ 3.3 million
State	$ 1.0 million

NIH numbers from 2001, and they are focused on the biologic sector. This does not include training, so it gives you an idea of the level of investment. You can see that Texas is doing extremely well. These are excellent numbers. This is an important engine for the state and reflects the state's wisdom in developing these academic institutions. We need to capitalize on this base. An example of how to capitalize would be the creation of the ability to transfer this technology into industrial parks. I favor development of a second Texas Medical Center for Industry, adjacent to the Texas Medical Center and the size of the Texas Medical Center. It is estimated such a campus would exceed the income of the Texas Medical Center within fifteen years. We are underachieving by almost tenfold the introduction of new corporations in the state based upon our investment. Before we rest on our achievements in our great state, there is competition to be considered. I have identified two substantial challengers—San Francisco and Boston. Their numbers (*Table 3*) are terrific. These are very powerful institutions that score beautifully in the ability of their scientists to draw in basic research numbers.

Table 2
Texas' 2001 Share of National Research Funds

Baylor College of Medicine	**$205,439,317**
M.D. Anderson	**$ 90,188,425**
Rice	**$ 4,436,938**
University of Houston	**$ 12,038,167**
Univ. Texas Houston	**$ 71,920,305**
Univ. Texas Austin	**$ 34,236,699**
Univ. Texas Southwestern	**$ 131,882,625**
Univ. Texas San Antonio	**$ 62,733,840**
Texas A&M	**$ 20,300,939 + $13,912,253**
Univ. Texas Galveston	**$ 61,319,476**

SOURCE: National Institutes of Health.

Table 3
Texas' Competition for National Research Funds in 2001

Univ. California San Francisco	$292,103,420
Stanford University	$204,766,474
Univ. California Berkeley	$ 78,245,614
Harvard University	$243,710,837
Brigham & Women's Hospital	$164,768,897
Boston University	$111,611,498
Dana-Farber Cancer Institute	$ 95,072,888
Whitehead Inst. for Biomedical Research	$ 91,914,328
Univ. Massachusetts Medical School	$ 77,018,828
Massachusetts Institute of Technology	$ 71,094,309
Children's Hospital (Boston)	$ 63,920,552

SOURCE: National Institutes of Health.

My favorite project on the West Coast is Mission Bay in San Francisco. It is the site of the old 1903 earthquake that has been reclaimed. This is a real estate-driven park. The funds are from the private sector. Everything from academic institutions to biotech clusters is located within it. Profit is made on the commercial side: commercial centers, townhouses, housing, hotels, and, incidentally, biotech parks in academic institutions. It is located adjacent to downtown. It is a beautiful opportunity for San Francisco to accelerate what is already a very powerful focus in the state.

The opportunities for expansion in our region are to increase the number of quality start-ups. We need to recruit pharma and biotech into our region, not just to grow them but to recruit them. We need to be looking for more opportunities for consolidation. The consolidations do not have to come out of Texas. We could take a Texas base and move a company from Seattle or Baltimore, for example. Consolidations are critical because of the large numbers of companies drifting down to smaller numbers of quality organizations.

It is clear that improvement in business plans and management is critical. The talent and skills are not at an optimal level in our state. To have talent and the opportunity for expansion, we need to build and recruit. We need larger VC investment firms. We need regional incentives such as is being done in Michigan, Ohio, Missouri, and others. I am extremely pleased with Governor Perry's initiative in the state of Texas. When you have the governor leading, others join the logic. His leadership has been critical. We are fortunate to have this leadership in the state. Finally, we need to advertise, advertise, advertise, and communicate with the VCs that are moving and driving biotech.

Table 4
Publicly Traded Biotech Corporations in Texas

Introgen ($95M)
Lexicon ($460M)
Luminex ($200M)
Tanox ($600M)
Texas Biotechnology ($250M)
Total: $1.605 Billion

Table 4 shows the Texas-based companies traded on the Nasdaq. All these companies are derivatives of academic institutions. The research engine of the institutions leads to the ideas that back these companies. We are doing well, but we can do better.

Lexicon Genetics, in The Woodlands, is an example of one of those Nasdaq-traded companies. It is now a 500-person pharmaceutical company. It has two divisions; the chemistry company is in New Jersey, and a biology division is in The Woodlands. Gordon Cain has to be given a lot of credit for this corporation. He stepped up to the plate to singularly fund the company. He told me several days ago he preferred single ownership. Few had his vision and resources. The public offering raised the necessary capital from the market to build a corporation in Texas and New Jersey. We can do more in Texas with leaders of the quality and confidence of Gordon Cain.

Let me finish with a few comments. First, we have abundant unsolved medical needs. The new technology enables innovative discovery. Second, we have an emerging set of new information from the genome project—all investigator empowering. Third, the biotechs can move faster and are more focused than pharmas. What are the challenges? I see the following challenges for biotech: Visualize your product. Manage the company to achieve that product. Value the product properly at the outset, and fund the company sufficiently to be able to drive to the end point you are trying to achieve in the development. Consistently look for the opportunity for consolidation, and wish good health to big pharma.