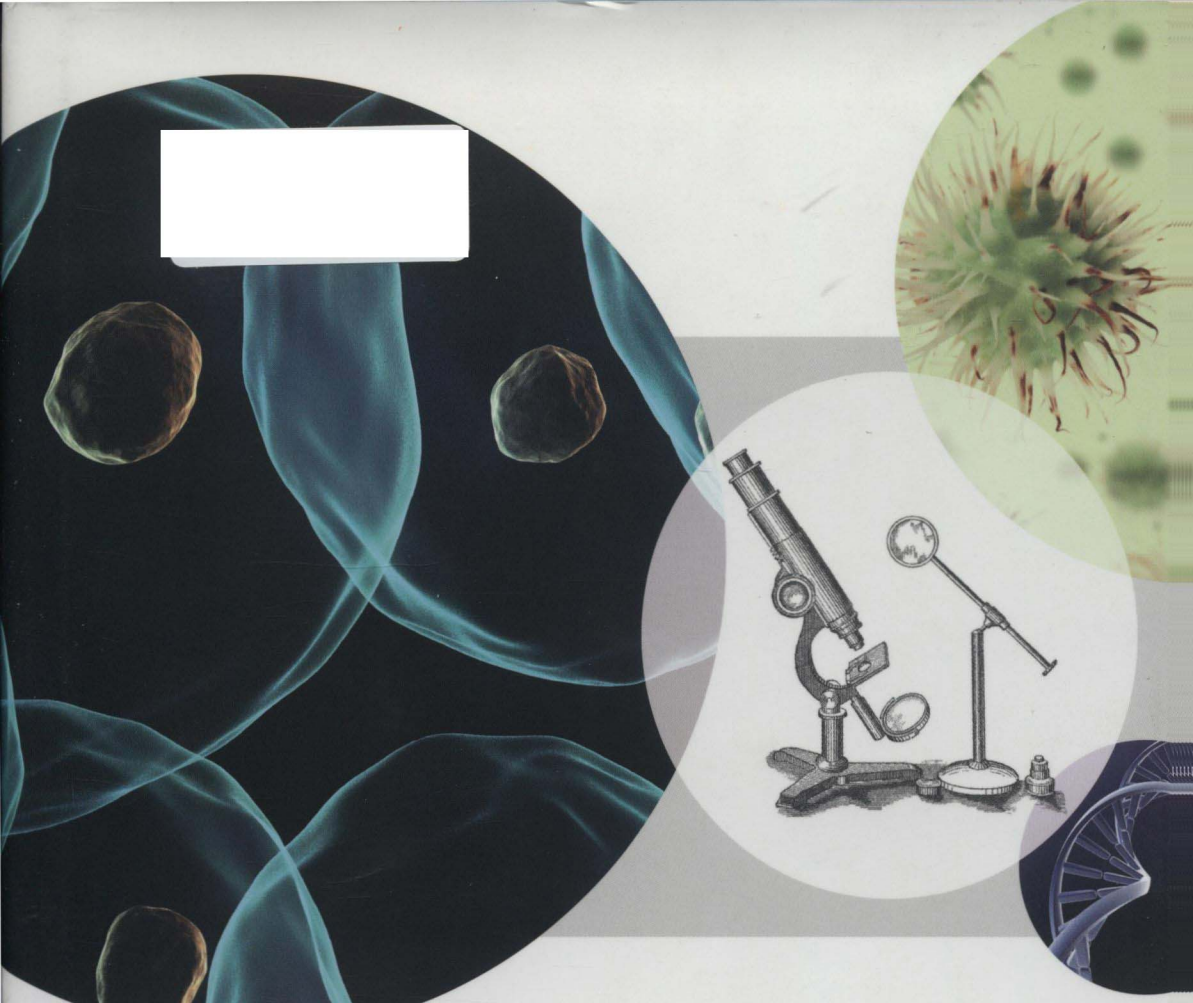

FROM X-RAYS TO DNA

HOW ENGINEERING DRIVES BIOLOGY

W. DAVID LEE

WITH JEFFREY DRAZEN, PHILLIP A. SHARP, AND ROBERT S. LANGER

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and Robert S. Langer

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From X-rays to DNA

This book is dedicated to my first wife, S. Ramsdell (Ramsey) Lee, whose fight against cancer opened my eyes and inspired me to become involved in cancer research and medical device development.

Preface

Born in the 1940s, I was one of those inexhaustibly curious children who built a laboratory in the basement of his house in Detroit. Complete with natural gas Bunsen burners, stocked with nitric and sulfuric acid and magnesium ribbon, I "experimented" with real chemistry. One very cold winter day, after filling the house with billows of chlorine gas (which forced the whole family to evacuate), my parents decided it was time for me to graduate to electronics and motors. My biggest accomplishment was building a motor that powered nothing!

My first exposure to organized scientific development was in 1966, when I spent the first of several summers as an "accelerator technician" at the Lawrence Berkeley Radiation Laboratory, known then as the "Rad Lab." It was invention and building experiments on a super grand scale and I was in my element there, surrounded by cyclotrons and other magnificent gadgets. In 1969, after graduating from MIT, I was hired by Arthur D. Little (ADL), a large, prestigious, technology-based consulting firm, where I was ultimately in charge of the technology and product development business. During my 25-year tenure there, we built from scratch nearly everything we worked on (cryogenics, combustion, appliances, space hardware, etc.). A principal investigator at ADL (called a case leader) would begin a project with a lab containing only empty benches. He or she would then proceed to design and build the equipment that would be the basis of the team's research. At ADL, I learned how to conduct research from Dr. Robert Wilson, Dr. Joan Berkowitz, and Dr. Peter Glazer. Bob taught me how to think through the design of an experiment, constantly refining the understanding until it could be summarized on a single page or, better yet, a 3×5 card. Joan taught me the ins and outs of chemistry, which I seemed to have missed in my years at MIT. Peter Glazer showed me how to reach out beyond the obvious and conventional and have the courage to propose new technologies; then relentlessly pursue funding until you are able to build what you dream.

After losing my first wife to cancer in 2003, I made a career change from hardware development to cancer research. I had the good fortune to know Professor Tyler Jacks, the director of the MIT Center for Cancer Research (CCR). Taking a huge risk, Tyler invited me to meet others at CCR. I had further luck in that MIT was in the process of formulating the concept of integrating engineering and biology in an effort to address cancer at what is now the MIT Koch Institute for Integrative Cancer Research. In 2008, I was offered a role at CCR to help with the interface between biologists, engineers, and clinicians. As I was being introduced around CCR, I was struck by the uniformity of the different biology labs. Of course, at that point, I did not understand enough of the subtleties to see the differences. I could not help comparing my then simplified view of biological research with my exposure to research in high-energy physics and so forth, where the key research tools were always purposefully built by the team concurrent with the design and conduct of the research. This seemed like a dramatic difference, and I questioned its importance. I looked for case studies that explored the integration of engineering and biology in an effort to accelerate the discovery and found nothing. I chatted with my friend Dr. Jeffrey Drazen, the editor in chief of the *New England Journal of Medicine*, about his observations, and he encouraged me to do my own primary research. Simultaneously, Phillip A. Sharp was writing about the convergence of the life sciences, physical sciences, and engineering. Conversations with him helped shape the theme of the book, and I was off and running.

Acknowledgments

It has taken many years, many minds, and much encouragement to get here.

From the very beginning of this project, I have had the unwavering support of Dr. Jeffrey Drazen (editor in chief of the *New England Journal of Medicine*) and two MIT Institute professors: Dr. Phillip A. Sharp and Dr. Robert S. Langer. The three brought such unique perspectives that I decided to include interviews with them in the book. I can say without hesitation that without Jeff and Phil's encouragement and time-consuming involvement over the past 3 years, I would not have completed the effort.

Unlike typical acknowledgments of wives who suffer the months and, in this case, years of neglect while the writer writes, my wife, Eve Youngerman, had the foresight and wisdom to choose to become an integral part of the effort and write a large part of one chapter. Eve was a consistent and reliable cheerleader. She was assisted in her research by our daughter, Ruthie Lewis, an undergraduate studying biochemistry.

After the initial draft, I worked with James Buchanan (Orchard Writing) on the structure, flow, and content of the book. James made big contributions throughout the book helping to craft more readable pages and improving the flow of the ideas. James was also a good teammate for when it seemed as though the book would never be completed: He was a positive force.

Along the way I had the fortune of receiving insight regarding themes and approaches from Dr. Andrey Zarur, managing partner of Kodiak Ventures, as well as from Dr. Robert Urban, then the executive director of the MIT Koch Institute and now at Johnson & Johnson. Andrey could in a matter of minutes picture the entire subject and suggest important thematic changes. I always value Andrey's suggestions. At the first complete draft, I enlisted my brother Kevin Lee, an attorney, to read the entire document. I have leaned on Kevin my entire life starting back on the playgrounds in Detroit so it seemed like a logical thing to do. I wanted to see if someone outside of the medical community would be interested in the material. He was, and he then made

important changes to the historical analysis. At the same time I got editorial comments from my longtime friend Terry Finn, also an attorney and outside of the medical community.

Once the draft was completed, I had the benefit of expertise from some talented people. Dr. Annetine Gelijns is the professor of health policy at the Icahn School of Medicine at Mount Sinai and a researcher and scholar on the subject of technologies in medicine. Annetine helped me correct some important logical errors and clarify my observations. I only regret not having started our collaboration earlier. Dr. Nadya Dimitrova, a postdoctoral student in the Jacks Labs at MIT, poured through the entire book, ensuring that the biology discussions were correct and consistent. Nadya did a remarkably thorough edit, which surprised me by the sheer number of corrections. Robert Lewis, my son and a Ph.D. candidate, also made suggestions and edits to improve the book.

While my two daughters, Katie and Merritt, did not research or write anything, their beaming smiles when I talked about my research findings for the book were a constant inspiration. My other son, Jamie, and my two sons-in-law, Jeff Fishbone and Kevin Garofalo, listened patiently as I droned on about my epiphanies. The biggest thanks, however, must go to my parents, Barney and Mary Lee. Their support of my insatiable childhood curiosity, encouragement of my early scientific explorations, and unconditional belief in my abilities have allowed me to achieve the successes in my life.

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INTRODUCTION

1 An Opportunity for Greater Discovery

For many in the developed world, the word *tuberculosis* conjures an image of a long-vanquished infectious disease akin perhaps to polio or smallpox. Tuberculosis is a disease that is beyond the memory of most, but it is a term loaded with potent symbols of its past virulence: sickened patients coughing up bloody sputum in sanatoriums.

The suffering caused by tuberculosis has vanished in the modern age, as have the many sanatoriums (isolated facilities for tuberculosis patients), which have been converted to historical landmarks or dedicated to other uses. To people in the United States and other developed nations, the fear produced by the threat of tuberculosis epidemics is a piece of historical ephemera.

By contrast, in developing nations such as Haiti, tuberculosis is a current and all too real fear. Prior to the earthquake in 2010, tuberculosis was second only to HIV/AIDS in terms of the number of deaths caused by infectious disease. In 2007, nearly 7,000 people in Haiti died of tuberculosis, and more than 29,000 Haitians developed the disease in 2009. Most of the country's infrastructure, which included numerous medical facilities, was destroyed. This in turn led to a diaspora of patients seeking shelter in numerous densely packed camps in and around the country's few cities. Countless others also left the ravaged population centers to find succor among their hometowns and villages. Making matters worse, without consistent access to treatment, sufferers likely developed and passed on drug-resistant strains of the disease.

In many ways, the earthquake took Haiti back to a time before modern health care systems had the tools properly to diagnose, treat, and cure this disease.

At the beginning of the nineteenth century, tuberculosis, known then as *pulmonary consumption*, was an endemic infectious disease. It could only be identified in its later stages after its most severe symptoms—bloody cough, night sweats, and extreme fatigue—clearly demonstrated its presence as distinguished from a number of other communicable diseases.

Medicine of the time simply lacked the tools to diagnose tuberculosis and the medicines to treat it effectively. This meant that each day was the equivalent of the tuberculosis diaspora of Haiti. Imagine living at a time when a simple ride in a horse-drawn carriage across town or to another city could bring you into contact with an individual whose only symptom is a persistent cough. As annoying as it may be, it would not be inconsistent to encounter many people each day with some sort of chronic or acute pulmonary ailment.

After arriving at your destination, you wish your fellow travelers well and then walk to work or home to your family and quickly forget the incidents of your ride and your companions. The only memory of it is captured in the tuberculosis bacteria you inhaled after your fellow traveler coughed and did not properly cover his or her mouth.

Over the next few weeks, months, or perhaps longer, the bacteria take up residence in the tissues of your lungs. In this fertile environment, they grow and multiply causing at first minor symptoms. Before long, though, you have developed a persistent cough that begins to produce bloody sputum. You have unaccountably lost weight, experience night sweats, and are bone tired.

You consult a physician, who, based solely on the report of these symptoms, diagnoses you with pulmonary consumption. The stethoscope has not yet been invented, so he does not have the ability to perform even a cursory examination of your lungs and heart. The notion that it is caused by bacteria is completely unknown to him. If you mention the coughing companion of your carriage ride, it would hold little meaning for your physician because he knows little about how the disease is contracted.

What he can tell you is that there are no effective treatments. If you have the money, you can seek comfort at a sanatorium, but most likely you return home to your family. Although some diagnosed with consumption manage to survive, it is very likely you will soon die. It is also highly likely that your family and friends, whom you have most certainly infected, will suffer the same fate.

Half a century later, the fate of the average consumption patient began to brighten. Working with one of the first compound microscopes sensitive enough to detect bacteria, Robert Koch identified the bacterium that causes tuberculosis. About 15 years later, the development of the Crookes tube—the device that helped identify electrons—led Wilhelm Roentgen to discover X-rays.

A few years later, X-ray technology was made commercially available to doctors and hospitals, which allowed doctors to diagnose tuberculosis before it became florid. This in turn allowed organized medical systems to better