Preface

I will ask you to mark again that rather typical feature of the development of a subject; how so much progress depends on the interplay of techniques, discoveries and new ideas, probably in that order of decreasing importance.

—Sydney Brenner

We are witnesses to—and beneficiaries of—a remarkable revolution in health care, especially in emerging new therapies and even preventions for a host of human diseases. Previously unimaginable cell- and gene-based therapies—such as the mRNA-based vaccines for COVID-19—seem to emerge daily. None of these advances would happen without biotechnology.

This book is about that technology: in particular, the basic science that drives it, and the people and companies who transformed that science into the biotechnologies we benefit from today and into the future.

This book is not intended to be a comprehensive history of biotechnology (a term first coined by Hungarian engineer Károly Ereky in 1919). It is instead more of a narrative of the stunning technological advances of molecular and cellular biology in the late twentieth and early twenty-first centuries, and their application to the development of the industry and its products—told through my lens on the companies that were set up to exploit them. I try to do justice to the contributions of many of the individual characters involved but cannot cover them all.

I also recognize that this topic is of great interest to many different people, from patients and their advocates to business entrepreneurs, scientists, and investors. I have chosen to provide descriptions of the technologies and some relevant anecdotes where appropriate, in separate boxes. I also try to define unusual and/or professional terminologies without interrupting the flow of the story I am trying to tell.

This book is a chronicle that reflects my very fortunate almost 50-year journey through the biotech business, including the companies and people I have met along the way. The story is most definitely not about me. However, the scope and content directly reflect my experiences, and I have kept the
narrative lively by incorporating various anecdotes and commentary in footnotes as we travel together.

**EARLY DAYS**

My journey started in the 1950s. When I was a child, I lived on Grimms Hill near Great Missenden in a county called Buckinghamshire, 35 miles west of London in England. When it rained, I used to go out to the road by the house and make sure the water could run down past the driveway without getting hung up by sticks and stones. On occasion I would redirect the water deliberately and see how long it would take for the water to remove the block. Sometimes, if it were late afternoon, I would see an older man walking up the road wearing a visor. One day I asked my father, a cancer research chemist at The Chester Beatty Cancer Research Institute at Pollards Wood in Little Chalfont nearer to London, who the person was. He told me it was Sir Robert Robinson, a synthetic organic chemist who had been awarded the Nobel Prize in Chemistry in 1947 for his investigations on plant products of biological importance, especially plant alkaloids. “One of the most eminent people you will ever meet,” my dad said.

Sir Robert lived at the top of the road in a house called “Lebanon,” I assumed owing to the cedar of Lebanon trees growing in the garden. I remember one day Sir Robert gave me a block of rock salt from Switzerland. I have no idea why—but it had a lasting impression on me. Couple that with living in a house with the journals *Nature* and *The Lancet* lying on the coffee table and I guess it is no surprise that both my sister Suzanne and I developed an interest in biology and chemistry from an early age.

Another important milestone was reading *The Chemistry of Life* by Steven Rose published in 1966. The diagrams of the molecules and the introduction to biochemistry totally captivated me, and a dog-eared copy became a close friend.

One week on a visit to see my father at the Pollards Wood labs, Roger Kirby (who is presently president of the Royal Society of Medicine in England) and I were allowed to extract nucleic acids from rat liver. Ken Kirby, Roger’s father who worked with my dad, had optimized a procedure

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That probably was true but not exclusively, as I got to meet and spend time with Sydney Brenner, who was probably the smartest molecular biologist there has ever been and certainly the smartest I have ever met.
of organic extraction using phenol m-cresol mixtures to isolate nucleic acids. After ethanol precipitation I spooled the isolated DNA on a glass rod and precipitated the RNA separately. From then on, I was hooked on labs, centrifuges, and nucleic acids.\textsuperscript{b}

I made the decision to read biochemistry instead of medicine at university. I was not that keen to treat ill people, which was what most doctors I met in the 1950s and 1960s did. The University of Birmingham accepted me: Samuel (Sam) Perry, an eminent muscle biochemist, was the Chairman of the biochemistry department. It was one of the best biochemistry departments in the country at the time, with a new dedicated six-story building.

After graduating with a degree acceptable enough to be qualified to do a PhD, I decided to learn some virology with Peter Wildy at the Medical School in Birmingham, where I completed the virology master’s programme. I learned about most of the DNA and RNA virus families, including those that infect plants. My PhD was entitled “mRNA Synthesis in Herpes Virus Infected Cells.” I did two years’ experimental work for it after finishing the MSc in the summer of 1972, and I received my PhD degree in November 1974. Like the work described in most PhD theses, the experiments and their conclusions were not really very good nor very insightful, but I learned a lot about how to isolate and work with RNA.\textsuperscript{c} I also learned about what “controls” were (i.e., controlling the vagaries of the experimental process by including different conditions).

I was never first in the class nor the best at anything that I did, but one learns to adapt to that. What I do have and always have had is energy, enthusiasm, and ambition. I have always made it a point to keep up to date with what is going on in the relevant research world around me by reading the literature assiduously. I have developed a deep appreciation and understanding of elegant experiments. Appreciating experimental elegance is an important motivator for a scientist, if only so one can reflect on how other scientists managed to do some of the amazing experiments that they did do. There are only certain skilled people who can either develop or can get complicated experimental techniques to work.

\textsuperscript{b}What a privilege it is to know what one wants to do at the age of 16 and to have had a lifetime doing it.

\textsuperscript{c}A fragile and interesting molecule that transfers information from DNA to protein as well as being intimately involved in the process of protein synthesis in a cell. Much more will be said about this molecule later in the book.
The PhD enabled me to get a job at the Animal Virus Research Institute in Pirbright Surrey (now the Pirbright Institute) to work on foot-and-mouth disease virus (FMDV) in the well-respected laboratory of Fred Brown. I learned about picornaviruses, published some reasonable papers, and got to spend a year in Eckard Wimmer’s lab at the State University of New York in Stony Brook on Long Island in October 1977. After my return from the United States to Pirbright in the autumn of 1978, I was in a perfect position to appreciate the importance of recombinant DNA (and monoclonal antibody technology) and to use those techniques myself.

**FORMAL BIOTECH JOURNEY**

My “formal biotech journey” started in late 1978, when we cloned FMDV RNA and made plasmids containing DNA copies of virtually the whole virus RNA. We were amongst the very first groups in the world to do that: we may even have been the first. I was also fortunate to form a collaboration with a research group at G.D. Searle in High Wycombe where they were cloning chicken ovalbumin cDNA. The large group at G.D. Searle not only provided the first research scientists for the first biotech company in the United Kingdom—Celltech—but later Searle scientists also started British Biotechnology. I joined Celltech in Slough in March 1983 and ran their cDNA cloning lab for several years.

In 1989 I moved to Glaxo Group Research, where we used recombinant organisms to screen for small molecules that affected a “drug target” and that perhaps could be developed into potential medicines after the application of the appropriate medicinal chemistry. Glaxo did some of the very first pharma–biotech deals. I subsequently moved to the United States in early 1993 to embrace genomics and “functional genomics” technologies at the biotech company Sequana Therapeutics in San Diego and run their R&D. Later, as the CEO, I led the company Structural GenomiX (founded in 1999) through its transition to SGX Pharmaceuticals in its exploitation of protein structure determination in drug discovery.

Human genome sequencing was a major focus for me at the National Cancer Institute (NCI)/SAIC-Frederick in Maryland, where I moved in 2006 after a brief stint at Novasite Pharmaceuticals, a G protein–coupled receptor company in San Diego. SAIC-Frederick was the company that ran

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My second daughter was the first “Celltech baby.”
the FFRDC (Federally Funded Research and Development Center) on behalf of the NCI. I looked after the Advanced Technology Program for them, which among other things had a big interest in genomics. My career then took me to “translational sciences” and cell and gene therapy at Biogen in Cambridge, Massachusetts in 2011, followed by working on haemophilia as EVP of R&D at Bioverativ, a Biogen spinout, in 2017. Finally, after the acquisition by Sanofi, I moved on to T-cell biology, CAR T cells, and related technology at Repertoire Immune Medicines in 2020. I am currently a venture partner at SV Health Investors.

**CHRONOLOGY AND CADENCE**

This book generally follows my own career chronology. The first three chapters describe the early days and the formation of the recombinant DNA–based companies on both coasts of the United States and in the United Kingdom. Chapters 4 and 5 trace the development of monoclonal antibodies (mAbs), the companies that were founded on this technological innovation, and the companies and leaders who developed some of the most important “blockbuster” monoclonal antibody products.

In Chapter 6, I draw on my experiences at Glaxo Group Research in the early 1990s to describe what pharma companies were beginning to do with these new technologies and the strategic alliances that they formed. It is also at about the same time that small-molecule drug discovery for common diseases—once the core strength of pharma—began to be done by biotech companies using combinatorial chemistry and screening. This led to new drugs for both old and new targets—some of which I describe.

Chapters 7 and 8 are organized around the astounding advances in genetics and genomics technologies and their applications in the last part of the twentieth century and into the twenty-first. I first describe some of the early excitement around cloning the genes causing the major forms of Mendelian inherited diseases, such as cystic fibrosis, Duchenne muscular dystrophy, and Huntington’s disease. Several companies were founded on these technologies,

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1 The United States and the United Kingdom were the centres for the development of biotechnology in the early 1980s, although there were some nascent company activities in the Netherlands, France, and Germany. This was as much cultural as it was access to the appropriate capital.
including Sequana Therapeutics, which would attempt to clone the genes involved in common diseases by this means. The Human Genome Project, and the public versus private race to sequence the human genome, is described, as it was responsible for many additional advances in biotech. However, rather than just revisiting a much-told story, I focus on the businesses involved, both “public” (e.g., The Institute for Genome Research [TIGR]) and private (e.g., Human Genome Sciences, Celera, and Incyte).

The inevitable turn to functional genomics, or the science of understanding the primary function of the genes associated with diseases, is the focus of Chapter 9. Several companies were founded on the premise that less complex organisms like fruit flies and worms would reveal the function of unknown genes of relevance to human disease. At the same time other scientists (and their new companies) turned to uncovering function by understanding the three-dimensional structure of proteins that employed crystallography technologies, but which were informed by a genomics-driven approach in order to facilitate drug discovery. Structural GenomiX (SGX), which was started in 1999, were a great example of such a company that I was fortunate to be able to help to build, as related in Chapter 10.

Despite business concerns expressed by traditional pharma, several companies emerged that were dedicated to applying genomics deeply to get insights into rare diseases, and more than a couple of companies were focused on finding and developing medicines to treat such diseases (e.g., Genzyme). I consider several of these—and their business models—in Chapter 11.

In pursuit of even greater understanding of molecular mechanisms in biology and disease, several academic scientists developed technologies that could reliably alter the expression of genes by blocking the translation of the mRNA copy of the gene into its designated protein. Chapter 12 covers these “antisense” and small interfering RNA (siRNA) technologies, the signature companies who were founded to blaze that trail, and the products that were made from the application of these technologies.

The grail of directly replacing or repairing a defective gene, colloquially known as “gene therapy,” contains the future-defining technologies of today’s biotech industry. I trace the halting beginnings of gene therapy to the present day in Chapter 13, focusing on both the technologies used and their applications and the activities of some of the many companies started in the space. Gene therapy segues into cell therapy (Chapter 14), where the early

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From strongly different points of view.
days mirror to some extent what happened in gene therapy. Important new companies have been and are still being formed, leading to the development of new cell therapy products such as CAR T cells for the treatment of hematological malignancies.

The most direct form of gene therapy—the ability to modify DNA sequences almost at will both in vivo and ex vivo—has exploded with the discovery and utilization of CRISPR-Cas 9 gene editing. In Chapter 15, I describe several companies founded on both gene-editing technology and locked in patent battles, as well as the earlier-developed DNA-editing technologies and the companies that exploited them.

I try to capture the impact of vaccines developed using biotechnological techniques on human health with some historical perspective in Chapter 16. Here I primarily focus on the diseases, mostly caused by viruses, to illustrate how biotechnology has influenced vaccine designs. Specifically, I consider several of the biotech success stories such as the development of hepatitis B and human papilloma virus vaccines, and I acknowledge the companies and people most responsible for developing them. In addition, and I hope without being too repetitious to what has already been published, I cover the development of the more recent vaccines against SARS-CoV-2, including the mRNA-based vaccines.

Biotechnology is not simply science and its successful (or not) application by innovative companies. There are many stakeholders, personalities, and events that can impact that success. Founders, finances, leadership, oversight, regulatory bodies, patient groups, employees, geography, etc., all demand attention and all play a role in success or failure. In the last two chapters I endeavour to capture the soul, or “essence,” of biotech, at least as I have assessed it over my journey through its peaks and valleys. In Chapter 17—Fortunes and Unicorns—I use many examples of different companies to illustrate the dark art of “valuation,” and the challenges of determining, justifying, and maintaining a high valuation, particularly as a “unicorn.”

The valuation discussion in turn sets the scene for Chapter 18—the Essence of Biotech—in which I define what I see as the primary “traits” that determine success or failure of companies in this industry (as demonstrated by the companies and technologies mentioned throughout the book).

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*A unicorn is a company with a valuation over a billion dollars. Remember, it does not always work out for many once-promising companies and technologies: sometimes they end in failure.*
Again, this is not a comprehensive review of technologies and companies, as it relies on my own experience for its structure and conclusions. As the lines between pharma and biotech have become increasingly blurred since the biotech industry started in the 1970s, this last chapter also includes thoughts on how things have changed or not changed. Ultimately, it is designed to leave you with more questions than answers about the future of the industry so you can think further about it.

PORTENTS

When I was considering writing this parallel of my journey with the history of biotechnology, I recalled a book entitled Invisible Frontiers by Stephen Hall about the race to clone the insulin gene. The book describes efforts to clone both a chemically synthesized insulin gene and one derived from mRNA as cDNA.\(^5\) The book was out of print, but I found a copy online from a secondhand bookseller in the Bay Area. It arrived on my doorstep in a nondescript and bedraggled wet package. The next morning when it was dry, I opened it to find that this copy of the book had been signed by all the principal founders and first employees of Genentech (see Plate 1). Ex-Genentech colleagues told me that there were in fact several dozen copies of the book that had been signed this way for Genentech employees involved in the insulin project. Presumably, this copy had been given away by someone who did not completely appreciate the importance of Genentech for the industry generally or of the principals who signed the book. I took this experience as a clear portent for me to get on and write this book. I hope you enjoy reading it and learning from it as much as I have enjoyed writing it.

REFERENCES AND NOTES