
Preface

The only approach to art is art itself.

— Klaus Eidam

The True Life of Johann Sebastian Bach

Research laboratories involved in studies on molecular genetic processes or on the development of diagnostic, prophylactic, and therapeutic tools for human diseases are all exceedingly familiar with the use of synthetic oligonucleotides or synthetic DNA. Today, the application of synthetic DNA is as common as the polymerase chain reaction (PCR), DNA sequencing, or nucleic acid hybridization. What used to be the exclusive domain for a limited number of research scientists only 20 to 25 years ago has now penetrated into many different applications in research and in health products in numerous laboratories and biotechnological and pharmaceutical companies. Originally conceived as a source of artificial genetic material, synthetic DNA has found major applications in many diverse nongenetic subject areas such as molecular diagnostics, microarray analysis, computer chip research, and antisense technology, to name only a few. Several factors have contributed to the current widespread use of synthetic DNA. Some of these factors may be directly related to the *convenience* of obtaining synthetic oligo- and polynucleotides, which have become readily available in large amounts because of the development of revolutionary techniques for DNA synthesis over the last three decades; however, the major factor that has contributed to the exponential growth and use of synthetic DNA is more related to the unlimited human *control* over the structure of synthetic DNA.

This notion should not be a surprise to readers. If we look closely at the history of humankind, we will understand that gaining control over the environment is the major adaptive mechanism used by humans. The evolution of humankind may be envisioned as breaking from the grasp of natural selection to embrace the implementation of rational development directed by humans. Science is used as a steppingstone to control nature for the benefit of humankind. Being archetypal to humans, this trend can be readily noted in many other fields of human activity. It is our craving to exercise control over our lives that has led to the development of an artificial world. For example, we have constructed artificial means for transportation such as automobiles and an artificial strictly controlled environment such as highways for the optimal use of automobiles. Consider modern homes, which are actually entirely artificial entities. They provide the same purpose as caves offered to our ancestors. However, a dramatic improvement in the quality of living found in modern buildings can hardly be disputed by anyone who lives in today's world and who may have had the opportunity to visit such caves, or who has a vivid imagination to picture such primitive residences. These simple examples show that the active process of gaining control over our life is, to a large extent, built on the development of artificial means that mimic nature's function without directly mimicking nature's ways.

Since life itself is predicated on nucleic acids as carriers of genetic information, nucleic acids as the subject of biological research best exemplify these trends of human activity in the biological sciences. We began to learn how to manipulate existing genetic material using genetic engineering techniques. However, only when we learned how to synthesize DNA of any sequence did real opportunities arise for generating an artificial, strictly controlled DNA world. It has opened new avenues for designing artificial genetic systems that will help avert harm's way and promote health and prosperity for humanity.

The very first attempt to chemically synthesize short oligonucleotides from nucleotides was performed in the laboratory of Dr. H. G. Khorana more than 35 years ago. The significance of this pioneering research in the biological sciences and its enormous potential benefit to the progress of humankind cannot be overstated or underestimated. These studies provided for the first time access to unlimited modifications of the genetic material opening a new era for the unrestrained manipulation of the DNA structure, which will ultimately lead to the creation of new artificial genetic systems with strictly predetermined properties.

History shows that artificial systems may result in producing similar problems as their natural counterparts. For example, cyberspace has created an opportunity for the generation of parasitic units of information such as computer viruses and worms that have found very efficient ways to replicate themselves at the expense of the entire system. We are just now at the doorstep of exploring the potential use of artificial genetic systems, and, as should have been anticipated, there are already the first signs that these systems may create their own successfully replicating parasitic genetic units (see Chapter 4). By creating artificial systems we create a new environment and a new opportunity for self-generation of parasitic units potentially harmful to this new artificial environment. This is not the first time, however, that we must balance progress in some areas of human activity against potential harm this progress may bring. "Understand the harm and benefit in everything" teaches Miyamoto Musashi, a philosopher, artist, writer, and peerless undefeated sword fighter from 17th century Japan, in his *The Book of Five Rings*. After putting his life on the line on numerous occasions in his quest for self-perfection, he came to understand the value of this notion and tried to pass it on to posterity as a piece of his wisdom.

During more than 30 years of research, synthetic DNA has been developed for use in many applications, some of which are described in this book. While the harm from using artificial DNA is still conceptual, we have already witnessed the invaluable fruits this new technology has brought to reality. Today, the list of applications for synthetic DNA is so lengthy that a cursory inspection of this list would take more time than the reading of this preface. The myriad uses for synthetic material are only limited by our own imaginations. As always, the best is still to come.

The history of research studies and applications of synthetic DNA is rather short. However, even a cursory analysis of the published literature reveals some intriguing trends. A literature search using the key words "oligonucleotide," "synthetic gene," "PCR," and "microarray" reveals very limited growth in the number of publications that used the word "oligonucleotide" at the beginning of 1970s. This growth leveled off throughout the 1970s and 1980s. However, in the late 1980s, the number of publications started expanding again, but this time growth occurred at an unprecedented rate until the early 1990s to a level where it was 20 to 30 times greater than in any other previous year. This dramatic increase was paralleled by an equally steep growth in the number of publications using the term "PCR." While the number of publications using the abbreviation "PCR" continued to increase until the turn of millennium, the number of publications using the word "oligonucleotide" declined in the mid-1990s, probably as a result of the less frequent use of this word in the context of PCR primers. This downward trend has been reversed in the last 4 to 5 years coinciding with a no less impressive growth in the number of articles using the word "microarray." What this simple analysis reveals is that the use of oligonucleotides over the last decade has been driven by the application of oligonucleotides to new technologies such as PCR, sequencing, and microarray.

The use of synthetic genes, however, has followed a very different trend. Unlike many other technologies, the application of synthetic genes did not rapidly expand after the construction of the very first one in the mid-1970s. The use of the term "synthetic gene" experienced a very mild increase in popularity around 1980 to 1981, but this blip on an otherwise flat line may be explained by the introduction of new efficient chemical methods for oligonucleotide synthesis, which made research studies on the synthesis and utility of long polynucleotides more affordable. Nonetheless, the number of publications quickly fell to zero within a couple of years. After the introduction of automatic synthesizers, which made synthetic oligonucleotides more available, the number of

publications reporting assembly of synthetic genes started increasing again. Later, the number of publications using the term "synthetic gene" experienced another mild boost by the application of PCR technologies, which significantly simplified obtaining long polynucleotides from short synthetic oligonucleotides. However, by the mid-1990s the number of publications began to decline once again.

Thus, while the use of synthetic oligonucleotides matured into various applications, all examples demonstrating an increased interest in synthetic genes were associated with oligonucleotide synthesis technology improvement and the development of new approaches to the synthesis of long DNA molecules, rather than on potential applications. The expansion on the use of synthetic genes has been hampered for years by the inefficacy of methods to assemble long polynucleotides. Despite the fact that the application of PCR has significantly improved the efficiency for the synthesis of long polynucleotides, the use of synthetic genes is still declining in popularity. Therefore, we must conclude that the use of synthetic genes is not yet application driven. Designing synthetic genetic systems requires novel integrated approaches based upon a "procreative" rather than "anatomical" course and a thorough understanding of the study subject. Do we have sufficient knowledge to rationally design and construct an artificial genetic world? Even if we do not yet possess such knowledge for many sophisticated applications, are we ready to explore a new world of artificial genetics? As this book proves, so much already has been done. But, how much will be done in the future! Breakthroughs may happen at any time. This is a very exciting area of molecular science that is on the very precipice of a scientific explosion waiting for new explorers. Join in!

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