SYNTHETIC BIOLOGY: GLOBAL MARKETS

BIO066D
January 2017

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ISBN: 1-62296-433-0

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CHAPTER 1
INTRODUCTION

STUDY GOALS AND OBJECTIVES

BCC Research's goal for this study is to determine the specific applications and forecast global market demand for synthetic-biology products over a five-year period from 2016 through 2021. Our particular interest is to characterize and quantify the synthetic-biology-product market potential by product type and end-use market segments. We also analyze the synthetic-biology industry structure, competitors and intellectual property landscape.

Synthetic-biology markets reviewed in this report include enabling products, biologic components, integrated systems and enabled products.

Our key objective is to present a comprehensive analysis of the current and future synthetic-biology industry, with an emphasis on products and technologies that are commercially important in the 2016 through 2021 period. Market segments with rapid growth rates are highlighted, as well as those segments with large market potential. This analysis provides a quantitative basis and market context for companies to make strategic choices about participation and how to compete in the synthetic-biology industry.

The study will be particularly useful to companies supplying synthetic genes and DNA constructs, oligonucleotides, DNA-sequencing products, bioinformatics, cell culture media, biofuels, specialty chemicals, cosmetics, flavors and fragrances, pharmaceuticals, vaccines, agricultural seeds, pest-control systems, microfluidics and life sciences tools.

REASONS FOR DOING THE STUDY

Synthetic biology has established itself as an important discipline within the life sciences industry. While there is enormous potential for future applications, synthetic biology also has a significant number of near-term commercial opportunities, and the list of new products and applications is continuously growing. Applications include specialty chemicals, enzymes, synthetic genes and cells, as well as pharmaceuticals, agricultural seeds, vaccines, biofuels and chassis microorganisms.

It is important for companies in industries impacted by synthetic biology to be able to sort through the many potential applications, to identify commercial opportunities for product development and competitive strategy. This report provides pertinent information to assist companies in prioritizing product opportunities and establishing a solid framework for strategic planning.

Synthetic biology affects a range of end-user industries including life science research, pharmaceuticals, energy, chemicals and agriculture. Because of its wide scope, synthetic biology plays an important role in the world's future industrial economy.

Continuing advances in enabling technologies such as DNA synthesis and sequencing, specialty media, genome editing and bioinformatics, as well as a need for more efficient microbial production processes, are driving the growth of the synthetic-biology market.

Developments in these multidisciplinary fields promise to advance the synthetic-biology industry and create unique market opportunities. This report analyzes these trends and their impact on the future markets for synthetic-biology products.

Based on these market and technology dynamics, it is especially timely to examine the current and future synthetic-biology markets.

CONTRIBUTION OF THE STUDY AND FOR WHOM

We have compiled a study of existing and future synthetic-biology products and technologies that will be commercially important in the main end-user segments of life science research, pharmaceuticals, energy, chemicals and agriculture.

We present markets by end-user segment (research, pharmaceuticals, energy, chemicals and agriculture) and by product type (enabling products, biologic components, integrated systems and enabled products). Key market segments are covered, including genome editing, synthetic DNA, DNA sequencing, chassis organisms, synthetic cells, production systems, pharmaceuticals, biofuels, chemicals and agriculture.

We analyze synthetic-biology technologies, growth-driving forces, market applications, industry structure and competitive dynamics, companies and industry alliances, future market potential and product sales forecasts for the period 2016 through 2021. We project the future use of synthetic-biology products in the main end-user segments and by product type.

This report will be of particular interest to companies in the industries of pharmaceuticals, chemicals, enzymes, energy, agriculture, bioinformatics, biotechnology and nanobiotechnology, as well as suppliers of genomics tools, genome-editing technologies and DNA-synthesis and DNA-sequencing products. It will also be of high interest to professionals within governments and regulatory agencies to understand the scope and pace of synthetic-biology technologies as they reach the market.

SCOPE AND FORMAT

The study scope includes core synthetic-biology products (synthetic genes, biobrick parts, delivery plasmids, chassis organisms, synthetic cells, production systems), enabling technologies (DNA sequencing, DNA synthesis and assembly, genome editing, bioinformatics and specialty media) and enabled technologies (biofuels, chemicals, pharmaceuticals, agriculture) that are already commercialized or are forecast to be commercialized within the next five years.

We analyze key synthetic-biology technologies and products to determine present and future market status, and forecasted growth from 2016 through 2021. We also discuss strategic alliances, industry structures, competitive dynamics, patents and market driving forces.

BCC Research examines the synthetic-biology industry by market segment, including the following segments: DNA sequencing; DNA synthesis; genome editing; synthetic-biology

foundries; industrial biotechnology; pharmaceuticals; and agriculture. The role of key strategic alliances and acquisitions from 2014 through 2016 is discussed. Emerging markets including synthetic genes, synthetic-biology-enabled drugs and vaccines, genome-edited crops, chassis organisms, as well as metabolically engineered factories for producing synthetic fuels and specialty chemicals are analyzed, and more than 135 companies in these fields are highlighted.

METHODOLOGY

BCC Research surveys key users and producers in each of the end-user market segments and technology fields that will be commercially important during the next five years. Discussions with industry thought leaders as well as secondary market research were performed.

Based on our analysis, we project the future applications of synthetic-biology technologies in the major end-user market segments and by technology type, and we forecast sales revenues for 2016 through 2021.

INFORMATION SOURCES

BCC Research performed primary and secondary research for this report. Primary sources included key industry companies and leading research institutions. In addition, data were compiled from secondary sources, including company websites and industry, trade and government publications.

RELATED BCC RESEARCH REPORTS

- BIO126B *Next Generation Sequencing: Emerging Clinical Applications and Global Markets*.
- BIO049F *Global Biochip Markets: Microarrays and Lab-on-a-Chip*.
- BIO059B *Epigenomics: Emerging Opportunities in Biomarkers, Diagnostics and Therapeutics*.
- BIO063C *Molecular Diagnostics: Technologies and Global Markets*.
- PHM044C *Personalized Medicine and Epigenomics: Technologies and the Global Markets*.

ANALYST'S CREDENTIALS

John Bergin is the author of previous BCC Research biotechnology reports: *Next Generation Sequencing: Emerging Clinical Applications and Global Markets*; *Epigenomics: Emerging Opportunities in Biomarkers, Diagnostics and Therapeutics*; *Global Biochip Markets: Microarrays and Lab-on-a-chip*; *RNA Interference in the Post-Genomics Era: Markets and Technologies*; *DNA Sequencing: Emerging Technologies and Applications*; *Biologic Imaging Reagents: Technologies and Global Markets*; and *Synthetic Biology: Emerging Global Markets.*

Mr. Bergin has held business development, sales and marketing positions with a Fortune 500 advanced materials company, as well as executive management positions with a nanotechnology/separations company. He holds a BS degree in Chemistry, an MS degree in Biotechnology and a Master of Business Administration.

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Chapter 2

SUMMARY

SYNTHETIC BIOLOGY: GLOBAL MARKETS

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CHAPTER 2
SUMMARY

In March 2016, researchers from Synthetic Genomics Inc. and the J. Craig Venter Institute completed the construction of the first minimal synthetic bacterial cell, dubbed Syn3.0. This synthetic biology milestone created a new artificial species containing just 473 genes. In October 2016, this synthetic cell line was launched commercially by SGI-DNA, an affiliate company.

The construction of Syn3.0 is only one of the most recent milestones in synthetic biology, a discipline that is transforming biotechnology, medicine and other industries, including chemical, energy and agriculture.

This report examines the dynamic synthetic-biology industry, including its technologies and global markets, and the leading companies in each of the market segments.

The synthetic-biology industry consists of three main sets of technologies and products: enabling, core and enabled. Enabling technologies and products are the engine that drives the development of the synthetic-biology industry. Core products and technologies — standardized DNA parts, synthetic genes and chassis organisms — are the key tools by which cellular factories and systems produce enabled products.

Products enabled by synthetic-biology tools — pharmaceuticals, chemicals, biofuels and agricultural — have large downstream market potential. Synthetic-biology technologies add value in each of these downstream industries. For example, synthetic biology has simplified the commercialization pathway for genome-edited crops in the agriculture industry and enhanced the availability, quality control and testing of novel synthetic genes in the drug development industry.

The table below summarizes the global market for synthetic biology, through 2021, by product type.

SUMMARY TABLE

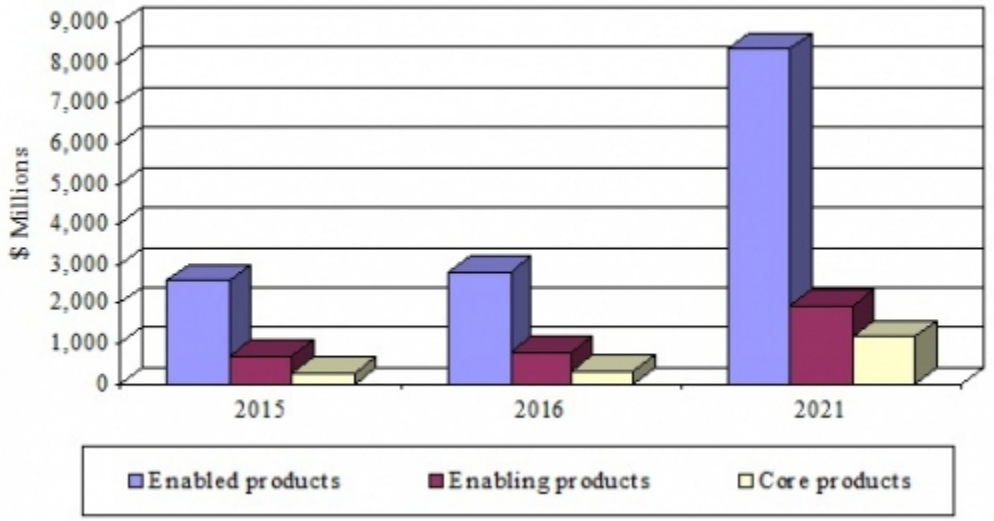
GLOBAL VALUE OF SYNTHETIC-BIOLOGY MARKET, BY PRODUCT TYPE, THROUGH 2021
($ MILLIONS)

Product Type	2015	2016	2021	CAGR% 2016-2021
Enabled products	2,593.5	2,800.6	8,336.8	24.4
Enabling products	692.3	786.0	1,914.5	19.5
Core products	262.5	311.5	1,158.7	30.0
Total	3,548.3	3,898.1	11,410.0	24.0

Source: BCC Research

SUMMARY FIGURE

GLOBAL VALUE OF SYNTHETIC-BIOLOGY MARKET, BY PRODUCT TYPE, 2015-2021 ($ MILLIONS)



Source: BCC Research

The global synthetic-biology market had a value of nearly $3.9 billion in 2016, and is growing at a compound annual growth rate (CAGR) of 24.0% to reach a forecast size of more than $11.4 billion by 2021.

Enabled products, the largest market segment, accounted for a value of over $2.8 billion in 2016 and is expected to grow at a CAGR of 24.4% to reach a forecast value of over $8.3 billion in 2021.

The enabled products segment is large and experiencing high growth, including in the fields of drugs, vaccines, bio-based chemicals, genome-edited crops and renewable fuels.

Growth is driven by a trend toward higher-value specialty products, such as performance chemicals, flavors and fragrances, drug/therapies and novel crop traits. This is driving growth in these markets.

The core products market segment is growing very fast — at a CAGR of 30% from 2016 to 2021 — due to increased demand for synthetic genes, the rise of synthetic-biology foundries and efforts by organizations including the BioBricks Foundation, DIYbio and SynBERC to develop and apply DNA constructs.

The enabling technologies market segment is continuing to innovate, for example, in the fields of gene synthesis and genome editing. Innovations in enabling technologies support the development of core products and enabled products.

The synthetic-biology industry concluded multiple strategic alliances during 2014 through 2016, illustrating the dynamic nature of this industry. Key trends include alliances by synthetic-biology companies to capture a larger share of the workflow value chain and alliances with end users in key industries, including pharmaceuticals, energy and

agriculture. This activity accelerates the practical applications of synthetic biology to a wide range of industries, further demonstrating the extensive reach of these technologies.

Chapter 3

OVERVIEW

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CHAPTER 3
OVERVIEW

SYNTHETIC-BIOLOGY TECHNOLOGIES COVERED IN THIS REPORT

The table below shows the scope of the technologies covered in this report. The main theme of the report is synthetic biology.

TABLE 1

SCOPE

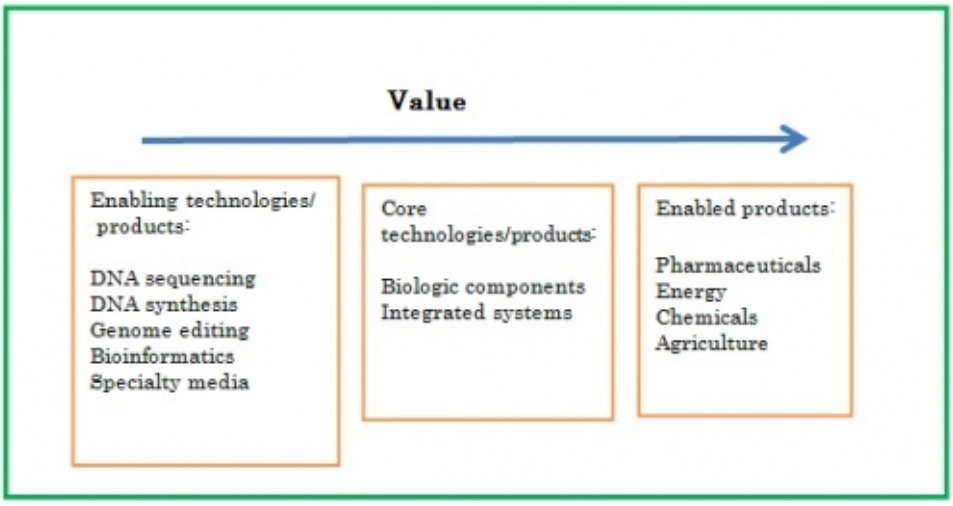
Technologies Covered in This Report	Technologies Not Specifically Covered in This Report
Synthetic biology	Systems biology
DNA synthesis	Genetic engineering
DNA sequencing	Cloning
Genome editing	Oligonucleotides
Gene synthesis	
Pathway engineering	
Minimal genomes and synthetic cells	
Biofuels, chemicals, agriculture, pharmaceuticals	

Source: BCC Research

The synthetic-biology industry is discussed using the value-chain concept. The figure below illustrates the synthetic-biology value-chain format used in this report.

FIGURE 1

SYNTHETIC-BIOLOGY VALUE-ADDED CHAIN



Source: BCC Research

Synthetic-biology-enabling technologies and products covered include DNA sequencing and synthesis, genome editing, bioinformatics and specialty media. The main synthetic-biology core technologies and products discussed in the report include biologic components (i.e., synthetic genes, delivery plasmids and BioBrick parts) and integrated systems (i.e., production systems, chassis organisms and synthetic cells). Synthetic-biology-enabled (i.e., downstream) products are covered including pharmaceuticals, energy (i.e., biofuels), chemicals and agricultural products.

Technologies that may be related to synthetic biology but are outside the scope of this report include systems biology, genetic engineering, cloning and oligonucleotides. The report does, however, contrast synthetic-biology technology with genetic engineering and cloning.

WHAT IS SYNTHETIC BIOLOGY?

Synthetic biology is an emerging field that uses standardized DNA building blocks (e.g., synthetic genes, etc.) to create value-added products with advanced functionality (e.g., bacterial cell bioreactors, etc.) to produce desired end products (e.g., drugs, chemicals, etc.).

There are three key producer groups in the synthetic-biology industry: those developing enabling technologies such as DNA synthesis and sequencing; those making DNA building blocks and integrated systems such as synthetic genes or minimal organisms; and those producing desired products using synthetic-biology platforms.

A key objective of synthetic biology is the use of standardized DNA-based building blocks to design cells for a specific purpose, such as producer cells to be used in cellular factories. To date, these producer cells are microorganisms (e.g., bacteria or yeasts). These synthetic-biology-derived cellular factories have advantages over conventional bioprocesses, such as higher yields, more flexibility in choice of feedstock materials, or lower cost.

In this report, BCC Research uses the following working definition for synthetic biology:

> Synthetic biology uses engineering principles to (1) design and construct new biologic parts, devices or systems, or (2) redesign existing natural biologic systems for a given purpose.

A principal objective of this report is to examine the scope of synthetic biology from a commercial standpoint. This means that the implications of the above definition are examined from both a technology and product standpoint. Synthetic biology encompasses a range of technologies ranging from gene synthesis to pathway engineering, and likewise the number of product applications is numerous and growing.

Synthetic biology is a core discipline in the life sciences industry, and encompasses many technical fields. It lies at the interface of genetic engineering, systems biology and nanobiotechnology.

Synthetic biology represents a major change in the scope of biotechnology. The existing paradigm of genetic engineering is to modify existing genetic material, cells or organisms, usually one gene or modification at a time. The paradigm change of synthetic biology involves applying engineering principles to biology to design new biologic systems for a particular purpose, often making multiple changes in parallel. Synthetic biology operates on a much more complex scale than genetic engineering.

Systems biology is related to synthetic biology because it studies interactions and relationships among different parts of biologic systems. For example, how do gene and protein networks influence metabolic pathways or cell signaling? Because synthetic biology seeks to construct biologic systems or parts thereof, understanding how the components of such systems interact is an important area of study.

Nanobiotechnology is related to synthetic biology since it studies biologic components of nanometer size. DNA, a key component of synthetic biology systems, has a diameter of 2 nanometers, and thus fits within the realm of nanobiotechnology. Synthetic biology provides a framework for developing nanobiotechnology in a more systematic way.

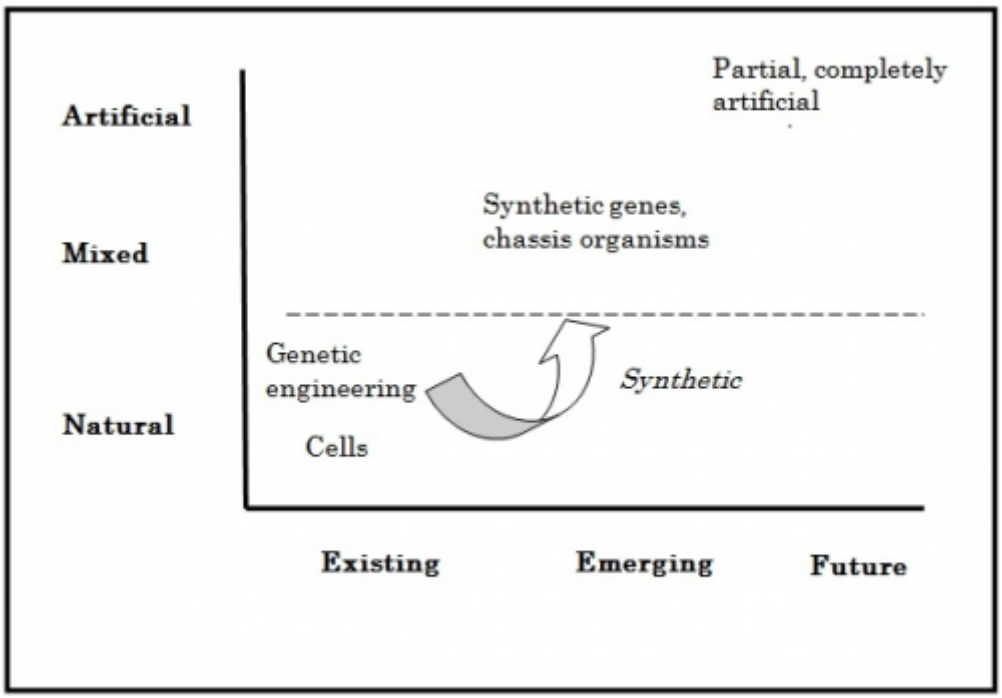
DEVELOPMENT STAGE OF SYNTHETIC BIOLOGY

Synthetic biology is an emerging technology that emphasizes artificial versus natural systems.

The figure below illustrates this concept.

FIGURE 2

FROM THE NATURAL TO THE ARTIFICIAL



Source: BCC Research

The natural world contains cells and their metabolic functions. Genetic engineering is an early mixed technology combining mostly natural components of a cell with one or more unnatural genes.

Synthetic biology takes a greater leap into artificial components and systems. Synthetic genes and metabolic engineering combine elements of natural (e.g., natural DNA sequence) and artificial (e.g., functional artificial genome constructs and synthetic minimal genomes) systems. Partially and completely artificial organisms move even further into the realm of the artificial, away from natural systems.

Instead of transplanting one gene into a foreign organism, synthetic biology inserts multiple genes that are designed to work together. These synthetic-genetic circuits allow scientists to coordinate multiple cellular processes simultaneously. An example of this is in biofuels, where metabolic pathways for cellulose digestion and for ethanol production are combined in a single microorganism. The genes are synthesized rather than extracted from the microorganisms, and their processes are coordinated to perform a complex cellular process.

Synthetic biology is on the leading edge of a transformation bringing biology and information sciences together. Many of the techniques and approaches used in information theory can be used in engineering of genetic circuits. This is because DNA consists of four bases, and cells read this code to decipher what molecules to produce and what actions the cell takes. The table below shows this concept.

TABLE 2

SYNTHETIC-BIOLOGY PARADIGM

Computer	Synthetic Biology
Code (1,0)	DNA (A,T,C,G)
Program	Genetic code
Software	Chromosomes
Hardware	Wetware
Computer	Cell

Source: BCC Research

Thus, synthetic biology can be compared with computers, but having a slightly different code. The computer uses codes (ones and zeros) to execute gates and transistors. The cell uses codes (A, T, C and G: adenine, thymidine, cytosine and guanine, respectively) to execute biochemical reactions.

Today, scientists are able to read the genome and put that information into a computer. Thus, synthetic biology is benefiting from megatrends in information technology as well as in life sciences.

FORCES DRIVING SYNTHETIC-BIOLOGY MARKET GROWTH

The table below shows key forces driving the growth of the synthetic-biology industry.

TABLE 3

SYNTHETIC-BIOLOGY GROWTH: DRIVING FORCES

Driving Force	Impact on Synthetic-Biology Markets
Emergence of advanced-generation DNA-sequencing and DNA-synthesis platforms	Increases the amount of genomic data available to synthetic biologies; easy access to DNA constructs; and easier synthetic-gene QC
Government support for renewable fuels	Mandates in many countries provide incentives for technical innovation and commercial risk-taking in use of renewable feedstocks
Rise of new genome-editing technologies	Enables rapid, easy and parallel genetic changes to be made to DNA, thus encouraging synthetic-biology approaches
Availability of synthetic-biology foundries	Provides access to the nonsynthetic-biology end-user community to new production pathways
Faster commercialization pathways emerging	Synthetic-biology tools have reduced the commercialization pathways in several industries including agriculture and pharmaceuticals

QC, quality control.

Source: BCC Research

Ongoing reductions in DNA-sequencing times and costs drive synthetic biology in several ways. First, DNA sequencing creates a large amount of electronic gene-sequence information, which is important for designing synthetic genes and biologic components. Genome databases are important starting points for downstream synthetic-biology applications such as protein expression, directed evolution and metabolic engineering. Second, low-cost DNA sequencing enables more efficient quality control of long DNA constructs, a key step in gene synthesis.

Reductions in the production costs of genes and their key raw materials — oligos — drives demand for synthetic-biology products. Synthetic genes are important to many synthetic-biology applications, and their availability at low cost increases the number of applications and customers, driving sales up.

Government support, particularly in the U.S. and U.K., is driving synthetic-biology growth in several ways. First, biomedical grants from large government funding agencies provide resources for basic synthetic-biology research, resulting in scientific innovation.

Second, government incentives (e.g., mandates, subsidies, tax credits and rebates) and initiatives in climate change and renewable fuels create a positive risk-taking environment for synthetic-biology companies to develop and implement biofuel strategies.

New genome-editing technologies, including cluttered regularly interspaced short palindromic repeats (CRISPR) and transcription activator-like effector nuclease (TALEN) systems, are having a significant impact on the synthetic-biology industry. These tools allow rapid, efficient ways to make changes to genomes, and thus improve the synthetic-biology workflow. In many synthetic biology development projects, high-throughput, simultaneous changes to a microorganism's genome allow for more rapid prototyping and testing of new microbial production systems. This development process is greatly aided by the new genome-editing technologies.

Synthetic-biology foundries design, build and test novel microorganisms for their suitability to manufacturing a specific end product. Foundries provide a range of synthetic-biology-related services to accomplish the objective of developing a new production process. The increasing availability of these services greatly aid end-user customers who may not have the synthetic biology skills required to accomplish these tasks by themselves.

Faster commercialization pathways are emerging as a driving force for growth in synthetic biology. For example, in the agricultural seed industry, genome-edited crops are not considered to be "genetically modified organisms" by the U.S. Food and Drug Administration. This is because genes are not being introduced from a foreign species, but only genetic material from the crop's own genome is used. This "non-genetically modified organism (GMO)" status significantly accelerates the regulatory process and thus the time to commercialization.

GLOBAL MARKETS FOR SYNTHETIC-BIOLOGY PRODUCTS

The table below shows the global value of the synthetic-biology market, by end-user industry, through 2021.

TABLE 4

GLOBAL VALUE OF SYNTHETIC-BIOLOGY MARKET, BY END-USER INDUSTRY, THROUGH 2021
($ MILLIONS)

End-User Industry	2015	2016	2021	CAGR% 2016–2021
Pharmaceuticals	1,843.6	2,004.0	5,358.9	21.7
Chemicals	1,240.6	1,359.8	3,855.8	23.2
Research	219.3	249.0	484.1	14.2
Energy	214.8	249.9	714.3	23.4
Agriculture	30.0	35.4	996.9	95.0
Total	3,548.3	3,898.1	11,410.0	24.0

Source: BCC Research

The total synthetic-biology market was almost $3.9 billion in 2016 and is forecast to grow at a compound annual growth rate (CAGR) of 24.0% to reach just over $11.4 billion by 2021.

Many of the market segments within the synthetic-biology industry are growing at a high CAGR due to growth of enabled products in the agriculture, chemical, energy and pharmaceutical industries.

The main end-user segments in 2016 include pharmaceuticals and chemicals, with market values of over $2.0 billion and just under $1.4 billion, respectively. Smaller segments include chemicals and research, followed by agriculture. Agriculture is a particularly high-growth market segment, as a result of increasing adoption of synthetic-biology methods in seed-development, insect-control systems and animal-breeding applications.

The total market size of just over $11.4 billion in 2021 reflects the growing penetration of synthetic biology into downstream markets, a result of the heavy research emphasis during the past 10 years.

The pharmaceuticals market segment is valued at over $2.0 billion in 2016 and is growing at a CAGR of 21.7% to reach a forecast value of just under $5.4 billion by 2021.

In the pharmaceuticals markets, synthetic-biology tools are indispensable to developing new drugs and production pathways. The increasing use of novel genome-editing tools such as CRISPR/Cas9 and TALEN is driving demand for synthetic genes and associated informatics, DNA sequencing and plasmid products.

In addition, more efficient synthesis routes for pharmaceuticals, including cephalosporins, diabetes and malaria drugs, and vaccines, is made possible by synthetic-biology platforms.

For energy and chemical applications, there is a need to establish and optimize economically viable bioroutes by using renewable feedstocks. In specialty chemicals, synthetic biology is becoming a useful tool for deriving novel products with improved function. These factors are driving the growth in these end-user industries.

The agriculture industry is projected to be a high user of synthetic-biology products in the future. In particular, genome editing is forecast to become a key tool for creating novel seeds due to its ease of use and non-GMO designation by regulatory authorities.

LIFE-CYCLE STATUS OF PRODUCTS AND TECHNOLOGIES

The table below shows the life-cycle stage of principal synthetic-biology products and technologies. The industry is diverse and covers a range of life-cycle stages from embryonic to mature.

TABLE 5

SYNTHETIC-BIOLOGY PRODUCTS AND TECHNOLOGY LIFE-CYCLE STAGE

Product Category	Principal Technologies	Life-Cycle Stage		
		Embryonic	Emerging	Mature
Enabling technologies	DNA synthesis; DNA sequencing; genome editing; bioinformatics; specialty media		X	X
Biologic components	Synthetic genes; biobrick parts; delivery plasmids		X	
Integrated systems	Chassis organisms; synthetic cells; production systems	X		
Enabled products	Production systems; novel synthetic genes		X	

Source: BCC Research

Enabling technologies and products can be considered a mix of mature technologies (e.g., specialty media and next-generation sequencing) and emerging technologies (e.g., genome editing).

Biologic components, including synthetic genes and biobrick parts may be considered emerging products and technologies. Technology for making synthetic genes is rapidly maturing, particularly for standard genes (short length, low guanine–cytosine content, etc.). However, for many complex genes and long DNA constructs, the technology is still emerging. In addition, biologic parts such as genetic regulatory switches are still emerging.

Integrated systems (i.e., chassis organisms, synthetic cells and production systems) are the most embryonic of the synthetic-biology products and technologies. The first minimal synthetic bacterial cell, JCVI-Syn3.0, was constructed in March 2016. This synthetic cell was designed and constructed from the bottom up, and it has been commercialized only recently as a research tool.

Enabled technologies and products may be considered as emerging if we look only at the synthetic-biology component of such technologies. This is usually a highly engineered microorganism designed with a particular feedstock and end product to be produced. If we are considering the end products, such as ethanol or specialty chemical, these are in the mature life-cycle stage.

The diverse life-cycle range of synthetic biology creates many niches in the industry for companies with different skill sets. For example, start-up companies with proprietary technology in DNA synthesis (e.g., Gen9 or Twist Bioscience) can establish attractive businesses in an otherwise mature industry. At the same time, established process companies (e.g., DuPont) can apply existing production and sales and marketing resources in mature end-market businesses such as polymers.

SYNTHETIC-BIOLOGY INDUSTRY

The table below summarizes the market focus of some of the key competitors in the synthetic-biology industry.

TABLE 6

SYNTHETIC-BIOLOGY COMPETITORS BY MARKET FOCUS

Synthetic-Biology Market Segment	Representative Companies
Enabling products	Thermo Fisher Scientific, ATUM (formerly DNA2.0), Origene (Blue Heron), Integrated DNA Technologies, GenScript, Gen9, Illumina, Cellectis, CRISPR Therapeutics, Editas Medicine, Intellia Therapeutics and Sangamo Therapeutics
Biologic components and integrated systems	Scarab Genomics, Ginkgo Bioworks, New England Labs, Codexis, DuPont, Novozymes, BASF, Synthetic Genomics and Zymergen
Enabled products – energy	TerraVia, Gevo, Global Bioenergies, Green Biologics, Aemetis, Amyris, Beta Renewables, Algenol, DuPont, Iogen and Joule
Enabled products – chemicals, agriculture	DuPont, Dow Chemical, Amyris, Glycos Biotechnologies, Gevo, TerraVia, BioAmber, Myriant, Genomatica, Evolva and BASF.
Enabled products – pharmaceuticals	Baxalta, Celgene, DSM, Johnson & Johnson, Juno Therapeutics, Kite Pharma, Novartis, Pfizer and Ziopharm

Source: BCC Research

Life science tools companies provide key enabling products to the industry, such as DNA sequencing, synthesis, genome editing, bioinformatics or cell culture media products. Key companies in this segment include Thermo Fisher Scientific, ATUM, Origene (Blue Heron), Integrated DNA Technologies, GenScript, Gen9, Illumina, Cellectis, CRISPR Therapeutics, Editas Medicine, Intellia Therapeutics and Sangamo Therapeutics.

The core products of synthetic biology include biologic components and integrated systems. Key companies in this segment include Scarab Genomics, Ginkgo Bioworks, New England Labs, Codexis, DuPont, Novozymes, BASF, Synthetic Genomics and Zymergen.

The enabled products industry is very fragmented, with more than 100 companies.

Several of the leading competitors with a focus on energy include TerraVia, Gevo, Global Bioenergies, Green Biologics, Aemetis, Amyris, Beta Renewables, Algenol, DuPont, Iogen and Joule.

Leading companies focusing on pharmaceuticals include Baxalta, Celgene, DSM, Johnson & Johnson, Juno Therapeutics, Kite Pharma, Novartis, Pfizer and Ziopharm.

Chemicals and agriculture companies include DuPont, Dow Chemical, Amyris, Glycos Biotechnologies, Gevo, TerraVia, BioAmber, Myriant, Genomatica, Evolva and BASF.

Chapter 4

SYNTHETIC-BIOLOGY TECHNOLOGIES

SYNTHETIC BIOLOGY: GLOBAL MARKETS

BIO066D
January 2017

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ISBN: 1-62296-433-0

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CHAPTER 4
SYNTHETIC-BIOLOGY TECHNOLOGIES

INTRODUCTION

SYNTHETIC BIOLOGY DEFINED

Synthetic biology is a broad term that encompasses a range of definitions, several of which are shown in the table below.

TABLE 7

SYNTHETIC BIOLOGY DEFINITIONS

Organization	Definition
Syntheticbiology.org	(1) Design and construction of biologic parts, devices and systems; (2) redesign of existing, natural biologic systems for useful purposes
COGEM	Design and synthesis of artificial genes and complete biologic systems, and changing existing organisms, aimed at acquiring useful functions
European Commission	Engineering of biologic components and systems that do not exist in nature, and the re-engineering of existing biologic systems; it is determined on the intentional design of artificial systems, rather than an understanding of natural biology

COGEM, Committee on Genetic Modification.

Source: BCC Research

Each of the definitions includes the construction and use of biologic components that do not exist in nature. In addition, some definitions include the redesign of existing, natural biologic systems. Another common component in the definitions is the application of engineering principles and rigor to the design and construction of biologic systems. A final component is the design of biologic systems for a specified, rational purpose.

Incorporating the above ideas, we arrive at the following working definition for this report as previously mentioned in Chapter Three:

> Synthetic biology uses engineering principles to (1) design and construct new biologic parts, devices or systems or (2) redesign existing natural biologic systems, for a given purpose.

A principal objective of this report is to examine the scope of synthetic biology from a commercial standpoint. This means that we will examine the implications of the above definition from both a technology and product standpoint. Synthetic biology encompasses a number of technologies ranging from gene synthesis to pathway engineering, and the number of product applications is numerous and growing.

HISTORY OF SYNTHETIC BIOLOGY

A brief history of synthetic biology is given in the table below. The foundations of synthetic biology were created in the 1970s, and during the 2000s the field grew rapidly.

TABLE 8

SYNTHETIC-BIOLOGY HISTORY

Year	Development	Commercial Significance
1970	Waclaw Szybalski coins the term "synthetic biology"	Provides a common language for this field
1977	Frederick Sanger publishes "DNA sequencing by enzymatic synthesis"	Seminal paper on DNA sequencing
1978	Nobel Prize given to Smith, Arber and Nathans for discovery of restriction enzymes	Discovery of key enzymes used for DNA synthesis and sequencing
	The first genome sequenced, PhiX174	Key achievement for DNA sequencing
1979	Khorana et al. synthesize the first gene (207 bp)	Key achievement for gene synthesis
1999	GeneArt, Blue Heron Biotechnologies founded	Gene-synthesis industry begins
2004	First synthetic-biology international conference at MIT	Recognition in academic community of importance of synthetic biology
2005	Chan, Kosuri and Endy synthesize bacteriophage virus, T7.1	First total synthesis of a virus, with 30% of its genome redesigned
	Synthetic Genomics, BioBricks Foundation founded	BioBricks Foundation records and indexes biologic parts used in synthetic biology; Synthetic Genomics is a pioneering commercial startup
	First iGEM competition	MIT begins the iGEM competition, encouraging students to create living systems for specific tasks
2007	DOE funds BioEnergy Research Centers	DOE commits over $375 million to fund centers, which will use synthetic biology as important research tool
2008	Synthesis of complete bacterium, *Mycoplasma genitalium* (582,970 bp)	Surpassed previous longest DNA synthesis by an order of magnitude; demonstrates proof of principle for synthetic genome
	iOWH, Amyris and Sanofi-Aventis agree to produce artemisinin	Commercialization process for synthetic biology's first drug product begins
2009	ExxonMobil commits $600 million to synthetic biology development	Marks entry by an oil major into synthetic-biology field
2010	Several corporate deals by pharma with synthetic biology-companies	Signifies potential of synthetic biology in pharmaceuticals and drug discovery and development

2011	Key acquisitions in food and farming markets	Demonstrates future value of synthetic biology to agriculture markets
2013	Synthetic Biology 6.0 held in London, U.K.	Leading synthetic-biology conference, held annually
2014	First complete synthesis of a eukaryotic chromosome, SynIII	Team from Johns Hopkins University and New York University achieve key milestone in synthetic-biology research
2015	Re-engineered yeast organism produces morphine opoids from sugar	Stanford University researchers insert genes from multiple different organisms into the yeast genome, creating a chassis organism capable of producing complex medicines
2016	Human Genome Project-Write proposed.	Large-scale initiative much like the original Human Genome Project would serve to drive development of new synthetic-biology tools and applications

bp, base pairs; DOE, U.S. Department of Energy; iGEM, Intercollegiate Genetically Engineered Machine; iOWH, Institute of OneWorld Health.

Source: BCC Research

Waclaw Szybalski first coined the term “synthetic biology” in 1970, giving the field a common language.

During the 1970s, fundamental work was done in synthetic biology enabling technologies of DNA sequencing and synthesis. In 1977, Frederick Sanger published a seminal paper entitled, “DNA sequencing by enzymatic synthesis,” which set the stage for the DNA-sequencing revolution. In 1978, Smith, Arber and Nathans received the Nobel Prize for their discovery of restriction enzymes, key tools for DNA synthesis.

Subsequently, the first genome was sequenced (PhiX174 in 1978) and the first gene synthesized (207 base pairs [bp] in length).

In the late 1990s, two gene-synthesis firms were founded: GeneArt (now Life Technologies) and Blue Heron Biotechnologies (now Origene).

In 2004, the first conference dedicated to synthetic biology was held on the campus of MIT. This was significant recognition by the scientific community of the growing importance of this field.

Chan, Kosuri and Endy synthesized the first virus, bacteriophage T7.1, in 2005. This marked the first total synthesis of a complete virus.

Synthetic Genomics, a spinout of Celera Genomics, was founded in 2005. In 2008, Synthetic Genomics synthesized the first complete bacterium, *Mycoplasma genitalium*, marking a key milestone in synthetic genomics. *M. genitalium* is a bacterium that causes bladder infections and is the smallest known genome of any free-living organism. This was a milestone for synthetic biology as it represented an order of magnitude longer DNA synthesis than previously had been done (52,000 bases versus over 500,000 base pairs).

The BioBricks Foundation was established in 2005. BioBricks is a nonprofit organization that catalogs synthetic biologic parts used in synthetic biology. In this role, BioBricks

provides a key database resource to the industry for constructing artificial biologic systems.

In 2005, the Intercollegiate Genetically Engineered Machine (iGEM) competition was initiated by MIT. iGEM is an annual global competition held to encourage undergraduate students to construct living systems.

In 2007, the U.S. Department of Energy committed $375 million to fund The BioEnergy Research Centers Program. These centers use synthetic biology to develop advanced biofuels.

Also in 2008, the first pharmaceutical product to result from synthetic biology, artemisinin, was given a commercial home by Sanofi-Aventis in a licensing agreement with the Institute for OneWorld Health and Amyris. This marks a milestone in commercialization of enabled products of synthetic biology.

In 2009, ExxonMobil formed an alliance with Synthetic Genomics to develop algal biofuels to replace biologic crude oil. As part of the agreement, ExxonMobil agreed to fund up to $600 million to support the development effort.

Several pharmaceutical-related deals in synthetic biology occurred in 2010. In October 2010, MorphoSys acquired the synthetic-biology company, Sloning BioTechnology. The benefit to MorphoSys is considered to be shortened lead times and higher success rates for antibody drug development.

Other drug-related deals in 2010 involved Roche and Evolva Holdings (drug discovery and development), Pfizer and MorphoSys (protein drug development) and Novartis and Synthetic Genomics (DNA vaccines).

In 2011, several industry acquisitions demonstrated the importance of synthetic biology in the food and farm markets. These included the acquisition of Abunda Nutrition by Evolva, DuPont’s acquisition of Danisco and Intrexon’s acquisition of Agarigen.

In June 2013, the sixth annual synthetic-biology conference, called Synthetic Biology 6.0, was held in London, U.K. This is the leading conference in this field and attracted scientists and companies from around the world for its annual meeting.

In March 2014, it was announced that a team of scientists from Johns Hopkins University and New York University succeeded in synthesizing a eukaryotic chromosome for the first time. The synthetic chromosome, called SynIII, is one of 16 chromosomes carried by the yeast *Saccaromyces cerevisiae*. SynIII was designed by using the third chromosome of *S. cerevisiae*, to which 50,000 bp were changed (out of 317,000 total bp). Changes included deletions, sequence additions and changed sequences. The researchers then used this design to construct SynIII. This synthetic biology milestone showed that a small team could design and synthesize a complete chromosome without using massive resources.

In August 2015, a team of researchers from Stanford University announced that the complete biosynthetic pathway found in the poppy plant for producing opioid molecules had been engineered into a yeast organism. To accomplish this, Professor Christina Smolke and her associates inserted genes from multiple organisms – including opium

poppy, Iranian poppy, California poppy, goldthread, bacteria and rat – into the yeast genome. The significance of this milestone is twofold: first, it was the most complex biosynthetic pathway engineered into yeast at that time; and second, it demonstrated the value of yeast as a chassis organism.

In June 2016, a group or leading scientists proposed a new large-scale synthetic-biology initiative: Human Genome Project-Write (HGP-Write). The HGP-Write would be a large-scale genome synthesis project that would use tools of synthetic biology: standardized gene parts, whole-genome synthesis and cluttered regularly interspaced short palindromic repeats (CRISPR)/Cas9 genome editing. The significance of this proposal is that, if it comes to fruition, it would serve as a driving force for multiple applications for synthetic biology in the future, much like the HGP-Read. In addition, a significant price drop in the cost of DNA synthesis would occur as a result of this project.

PARADIGM SHIFT IN BIOLOGY

Synthetic biology is causing a fundamental shift in thinking about biology and creating new paradigms, as shown in the table below. The conventional paradigm of using what is pre-existing in nature and continually evolving has been replaced by a new paradigm of using synthetic, engineered and disposable biologic parts and systems. This paradigm shift is creating new opportunities for technology development and products in such industries as life science, industrial biotechnology and pharmaceuticals.

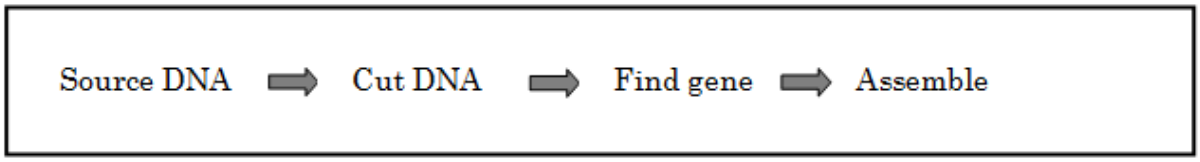
TABLE 9

PARADIGM SHIFT CAUSED BY SYNTHETIC BIOLOGY

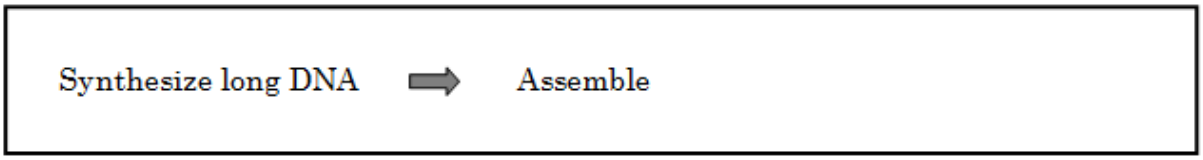
Traditional Paradigm	New Paradigm
Pre-existing	Synthetic
Natural	Engineered
Evolving	Disposable

Source: BCC Research

An example of this paradigm shift has occurred in the gene-synthesis industry – a branch of synthetic biology. The conventional approach to gene synthesis has been:



The synthetic-biology approach is:



This approach allows scientists to efficiently and cheaply synthesize large DNA pieces (greater than 10,000 bp) and assemble the long pieces into complete genomes for novel applications. The genes that can be used in these constructs do not have to be naturally occurring sequences, but can be completely novel, taking us into the realm of engineered, synthetic biologic systems that can function as cell factories, for example.

Today, using organisms as cell factories to produce valuable biologic and chemical products requires laborious and time-consuming effort to manipulate genes, one bp at a time. Synthetic biology provides a leap forward by allowing the design of genes with the most efficient coding and regulatory information. The resulting synthetic gene expresses an optimized protein product. The availability of synthetic-gene building blocks from several different organisms allows design of complete metabolic pathways for use in cell factories.

Another part of the paradigm shift is synthetic biology's use of engineering language and an approach of using standardized cells and components analogous to circuitry. This shift marks the movement of biology toward an engineering discipline.

The table below compares synthetic biology with genetic engineering – a well-established, mature molecular-biology technique for over 30 years.

TABLE 10

GENETIC ENGINEERING AND SYNTHETIC BIOLOGY COMPARED

Characteristic	Genetic Engineering	Synthetic Biology
Number of genes involved	One or a few	Many
Origin of genes	Naturally occurring	Naturally occurring; modified naturally occurring; or artificial
Diversity of resulting protein products	Low	High
Production of end products	Molecular cloning	Metabolic pathway engineering
End products	Proteins, simple chemicals such as ethanol	Proteins, small-molecule drugs, specialty chemicals and fuels
Technology life cycle	Mature	Maturing

Key tools used	Cloning, PCR, NGS	NGS; next-generation DNA synthesis; advanced gene-editing technologies; next-generation cloning and gene assembly; optimized hosts and specialty media for biofactories; and advanced software

NGS, next-generation sequencing; PCR, polymerase chain reaction.

Source: BCC Research

Genetic engineering involves the transfer of individual, naturally occurring genes from one species to another. Synthetic biology involves multiple genes, or gene cassettes, which may be either naturally occurring, modified naturally occurring or completely artificial. Synthetic biology assembles novel genes, gene clusters or genomes from a standardized set of genetic parts. Genetic parts include genes existing in nature that are being applied for a new purpose or redesigned, or novel, artificial genes designed and synthesized from starting chemicals.

Protein engineering and DNA shuffling are complementary technologies that allow scientists to change the amino acid structure and function of proteins that are expressed in microorganisms. These techniques create mutants (either by design or randomly) beginning with naturally existing organisms. Synthetic biology is very open to protein engineering because specific amino acids may be changed by altering the corresponding gene’s DNA sequence. This gives synthetic biology much greater protein diversity than genetic engineering.

Compared with genetic engineering, synthetic biology exerts a strong multiplier effect in the genetic constructs that are used and in the resulting protein products. This is because synthetic biology is not limited to one naturally occurring gene. Synthetic biology is a more complex technology than genetic engineering. For example, in genetic engineering, one gene is inserted into an existing biologic system, whereas synthetic biology works with several genes, whole metabolic pathways or even genomes. A second level of higher complexity is the use of both natural and unnatural genetic constructs in synthetic biology.

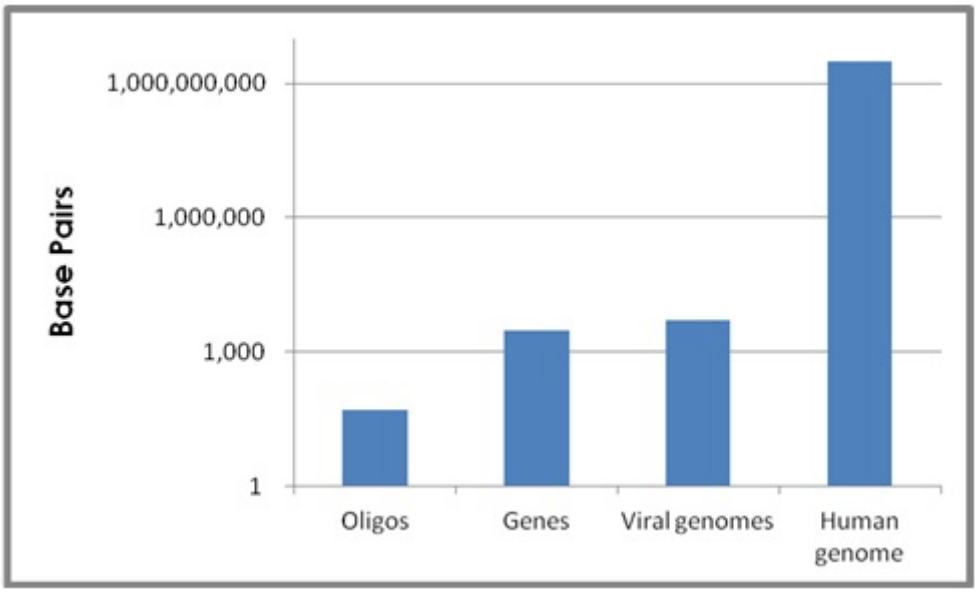
The products resulting from genetic engineering are mostly proteins or simple organics such as ethanol. Synthetic biology produces DNA, proteins, a wide range of value-added organic chemicals and biofuels, among others.

How do the two technology platforms express their desired products? Genetic engineering uses molecular cloning, which involves the replication of single genes in plasmids, after which it is expressed in bacteria or yeast cells to produce the desired protein (e.g., insulin).

Synthetic biology, on the other hand, uses tools such as pathway engineering to enable microorganisms to perform complex, multistep syntheses of desired products. Engineering involves assembling genes that code for each of the enzymes in a desired synthetic pathway. Other tools include: novel subsystems for next-generation cloning and assembly; biofactories that incorporate optimized hosts and specialty media; and software for in silico design and predictive modeling. Thus, the synthetic-biology industry offers significant opportunities for the suppliers of these enabling tools.

FIGURE 3

SCALE OF SYNTHETIC BIOLOGY



LEGEND
(%)

	Base Pairs
Oligos	50
Genes	3,000
Viral genomes	5,000
Human genome	3,000,000,000

Source: BCC Research

There is a great deal of scale difference among various DNA fragments that are used in biology. The figure above shows the scale of DNA fragments, which ranges from oligos to the human genome. Oligos are usually 10 to 100 bp in length, whereas a gene can range from 1,000 bp to over 3,000 bp. Whole genomes range from several thousand bp (viral) to 3 billion bp (human). The scale of synthetic biology is vastly greater than genetic engineering given that multiple genes, metabolic pathways and whole genomes are involved. Since the DNA fragments used in synthetic biology are much longer and more complex, DNA-synthesis technologies and costs are crucial to having a commercially viable synthetic-biology industry.

The shift from producing short-length DNA (oligonucleotides) using specialized instruments to long-length DNA for synthetic biology is driven by two factors. First is the technology to assemble short oligonucleotides into long-length DNA to construct genes or even whole genomes. Second is the emergence of companies that can synthesize long-length DNA at affordable prices. The costs for synthesizing a gene continue to decline at a very rapid rate, as we will show in a later section.

SYNTHETIC-BIOLOGY TECHNOLOGY OVERVIEW

Synthetic-biology technologies include enabling, biologic components, integrated systems and enabled. A summary of the products in each technology class is given in the table below.

TABLE 11

SYNTHETIC-BIOLOGY APPLICATIONS BY TECHNOLOGY

Technology	Description	Examples of Product Classes
Enabling	Technologies that are necessary for development of synthetic-biology products	DNA synthesis; DNA-sequencing instruments and reagents; microfluidics; advanced cloning and expression assays; specialty media for biofactories; bioinformatics
Biologic components	Artificial biologic macromolecules and genetic components	Synthetic genes, synthetic functional DNA constructs, synthetic DNA parts (BioBrick/iGEM),
Integrated systems	Artificial biologic systems that perform a specific function	Synthetic chromosomes and genomes; cells; biofactories; chassis organisms
Enabled	Products enabled by synthetic-biology tools	Chemicals; pharmaceuticals; biofuels; synthetic genes; synthetic cells; gene-edited seeds

iGEM, Intercollegiate Genetically Engineered Machine.

Source: BCC Research

Enabling technologies include those that are needed for developing or producing synthetic-biology products. For example, DNA-sequencing instruments and reagents are required for ensuring that synthetic-gene products incorporate the intended DNA sequence. Other enabling technologies include microfluidics, DNA synthesis, specialty media for biofactories and bioinformatics.

Biologic components are synthetic DNA, which can comprise complete gene, functional DNA construct or DNA parts (also called BioBrick and iGEM parts). Components are the nuts and bolts of synthetic biology, used to construct integrated systems and cell factories for producing enabled products.

Integrated systems include synthetic chromosomes and genomes (including microorganisms containing minimal genomes), synthetic cells, chassis organisms and synthetic organisms. Integrated systems perform specific, complex functions.

Enabled products include those enabled by synthetic-biology tools. This may include products that are discovered using synthetic biology, such as novel pharmaceuticals, or products that are produced by synthetic-biology-enabled cellular factories, including pharmaceuticals, biofuels, or specialty chemicals.

ENABLING TECHNOLOGIES

The table below describes five enabling technologies that play an important role in the synthetic-biology industry: DNA synthesis and assembly, next-generation DNA sequencing, specialty media, microfluidics and bioinformatics. These technologies create the critical mass required for the field to progress and mature. They are often provided by life science tool companies.

TABLE 12

IMPORTANCE OF ENABLING TECHNOLOGIES

Enabling Technology	Importance to Synthetic Biology
DNA synthesis and assembly	Construction of genetic building blocks: long DNA sequences, genes, gene clusters, genomes, gene libraries and chassis organisms
Next-generation DNA sequencing	Quality control of DNA-based products; growth in sequencing databases drives new applications
Specialty media	Ensures the viability of cellular biofactories
Microfluidics	Important component of DNA synthesis and sequencing
Bioinformatics	Needed for gene design and assembly; DNA sequence analysis drives new applications

Source: BCC Research

Continuing advances in DNA synthesis and assembly technologies are essential for constructing complex genetic building blocks in a low-cost, rapid and efficient way. Advanced DNA sequencing is required for quality control of the DNA-synthesis process. Specialty media are needed to grow and maintain biofactories. Microfluidics is a key component of advanced DNA synthesis and sequencing technology platforms and is essential to driving their costs down. Bioinformatics drives new synthetic-biology applications and is essential for the design of synthetic genes and other biologic parts and systems.

DNA-SYNTHESIS AND DNA-SEQUENCING COST TRENDS

The costs of DNA synthesis and sequencing are rapidly declining, particularly subsequent to 2002 when the next-generation sequencing (NGS) methods were first introduced. This cost reduction trend is critical to the market growth and adoption of synthetic-biology products.

This trend is illustrated in the following table, which shows the cost of sequencing a single human genome, from 2001 through 2015.

TABLE 13

COST TO SEQUENCE A SINGLE HUMAN GENOME, 2001-2015
($)

Year	Single-Genome-Sequencing Cost
2001	95,000,000
2003	40,000,000
2005	14,000,000
2007	7,000,000
2009	70,000
2011	8,000
2013	5,000
2015	1,000

Source: BCC Research; NHGRI Genome Sequencing Program

In 2001, sequencing of the first human genome was completed at a cost of $95,000,000 and over a period of three years. Since then, NGS technologies have rapidly progressed, making it possible to sequence an entire genome in 2015 for a cost of $1,000 in a few days.

These improvements have expanded sequencing from being a tool that was used in large genome centers for research to one that can be used in diagnostics and other applied applications.

Progress in reducing the cost of the sequencing itself has been truly remarkable, and now, for many applications, the actual sequencing costs is not as important a factor as the sample preparation and data handling and analysis costs.

The table below shows the historical costs for synthesizing single-stranded DNA (ssDNA) and double-stranded DNA (dsDNA) during the past 10 years.

TABLE 14

DNA-SYNTHESIS COSTS, 2006 AND 2016
($/bp)

	2006	2016
ssDNA	0.25	0.05
dsDNA	1.00	0.17

bp, base pair; dsDNA, double-stranded DNA; ssDNA, single-stranded DNA.

Source: BCC Research; www.synthesis.cc

DNA-synthesis costs, while reducing during the past 10 years, have not seen as dramatic a change compared with DNA-sequencing costs. The average $/bp for ssDNA (oligos) went from $0.25 to $0.05 from 2006 to 2016. The average $/bp for dsDNA (genes) went from $1.00 to $0.17 during the same period.

The cost of DNA synthesis is being reduced due to multiple factors, including next-generation synthesis methods using microfluidics and market demand growth in synthetic-biology applications.

Two potential future drivers of cost reduction in the DNA-synthesis business are large scale initiatives such as the HGP-Write, and the materialization of large markets such as DNA storage.

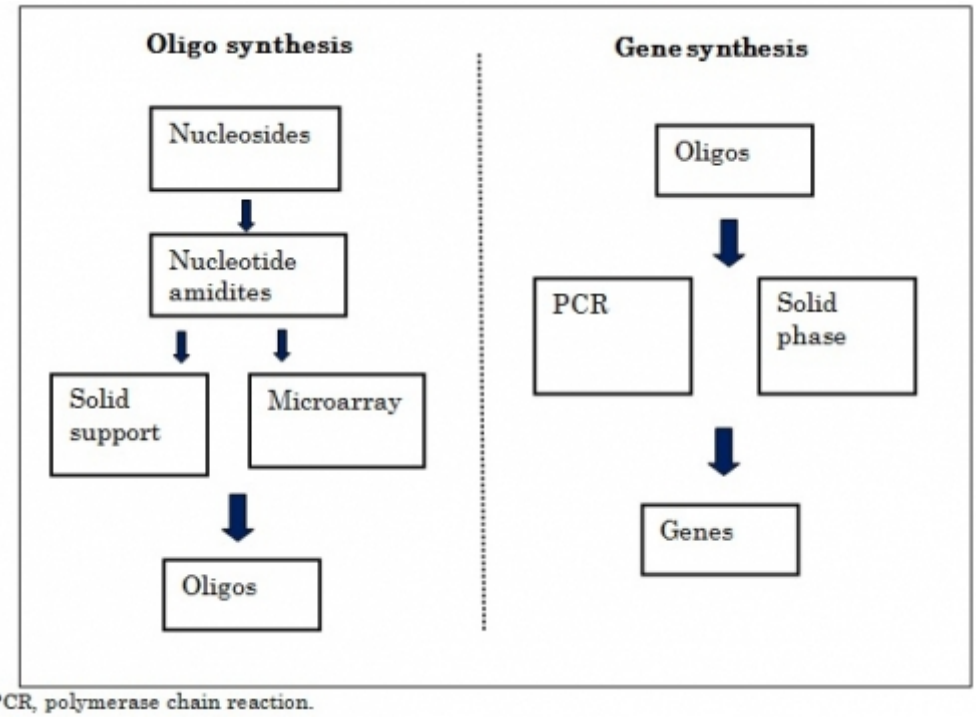
The overall impact of cost trends for both DNA sequencing and DNA synthesis are favorable to the synthetic-biology market.

DNA-SYNTHESIS TECHNOLOGIES

DNA synthesis is important to synthetic biology because many of the components rely on this technology, including genetic building blocks: long DNA sequences, genes, gene clusters, genomes and gene libraries. The figure below shows schematically the methods for synthesizing ssDNA (oligos) and dsDNA (genes).

FIGURE 4

SCHEMATIC OF DNA-SYNTHESIS TECHNOLOGIES



PCR, polymerase chain reaction.

Source: BCC Research

Oligonucleotides are key intermediates used in the gene-synthesis process, and their availability, quality and cost are important competitive factors in synthetic biology. Nucleotides are key raw materials used for DNA synthesis, and they are made by adding phosphate groups to nucleosides. In the past, nucleosides were isolated from natural sources (e.g., fish mullet) by a long and laborious process. Today, alternative sources of nucleoside production are available. Multiple companies in Asia now synthetically

manufacture nucleosides in high quantity and at low cost using cane sugar as the starting material.

From the nucleoside, nucleotide amidites are produced for use in automated DNA synthesizers. High-quality amidites are essential for successful synthesis of DNA.

Oligos are produced from nucleotide amidite building blocks using automated solid-phase synthesis. In solid-phase synthesis, the DNA polymer is constructed on solid beads in columns, one nucleotide at a time, with washing steps in between. The solid phase is important because it allows reasonable yields for a multistep synthesis process (i.e., a 20-nucleotide long oligo requires approximately 80 individual steps).

Achieving a high yield for each step in the process is an important consideration in oligo synthesis – for example, if each step in a six-step synthesis is 95% efficient, the overall yield would be only 73%. The main impurities in oligo synthesis are unreacted starting materials and n–1 products (i.e., one nucleotide too short). Using a solid phase is important because unreacted starting materials can easily be washed away, and a large excess of starting materials can be used to drive the polymerization reaction to completion. Most producers achieve single reaction efficiencies of greater than 99%.

The polymerization reaction cycle includes four steps (with washes in between): (1) deprotection to remove a chemical group that prevents premature reaction; (2) coupling during which a new nucleotide is added to the growing chain; (3) oxidation to stabilize the linkage of the chain with the newly added nucleotide; and (4) capping of partial products. This cycle is repeated multiple times depending on the length of the desired oligo product. When the growing chain has reached the desired length, it is cleaved from the bead.

Microfluidics and microarray-based technologies developed originally for gene expression are an alternative to the solid support methods and can be used for producing oligos in a massively parallel, automated process.

Next-generation DNA synthesis uses microarray technologies. Oligonucleotides are synthesized at high density on the surface of a chip, and these can then be used as starting DNA for assembly into longer synthetic genes.

The quality, purity and length of oligos affect their performance in gene synthesis. Errors result in undesirable mutations and increase costs because error correction is expensive and time consuming. The length of the oligo affects the quality (error rates) of the final DNA-synthesis product. Oligo lengths vary from 20 bp to 100 bp. Shorter oligos have fewer errors but higher gene-production cost due to more overlapping sequences. Longer oligos have more errors but lower gene-production costs.

Once the oligos are prepared, the gene can be assembled, and the table below compares the various technologies for doing this. The approaches can be classified as either polymerase chain reaction (PCR)-based (i.e., assembly PCR or in situ microarray) or solid phase (i.e., solid phase or convergent).

TABLE 15

COMPARISONS OF GENE-SYNTHESIS TECHNOLOGIES

Technology	Advantages	Limitations
Assembly PCR	Simple to use; multiple published protocols	Error rate 1:300; mismatched hybridization; some sequences not possible for PCR
In situ microarray synthesis	Potential for reduced costs and large-scale synthesis	Emerging technique; technically complex; limited by quality of oligos
Solid-phase assembly	Simple reaction; automated	Applicable to any sequence; simplicity; ease of automation
Convergent assembly	Relies on a series of simple, reliable reactions; not sequence dependent	Slower and more expensive than PCR; requires significant bioinformatics input

Oligos, oligonucleotides; PCR, polymerase chain reaction.

Source: BCC Research

PCR-Based Approaches

The assembly PCR approach involves using multiple oligonucleotides with short overlapping segments that cover the desired sequence on all or parts of both strands. The oligonucleotides alternate between sense and antisense directions. Overlapping segments dictate the order of the PCR fragments and thus produce the specified long DNA product. The oligos are pooled together and PCR amplified. Oligos are then cloned into a plasmid vector and cloned, and larger fragments are assembled by fusion PCR of other methods. Variations on this method include using a ligation step prior to amplification and secondary amplification with outside primers.

This approach is simple to use, with many published protocols. Many gene-synthesis companies employ this approach. Limitations arise from difficulty of using PCR for some sequences (due to high guanine–cytosine [GC] content, repetitive regions, etc.), which prevents synthesis or adds to the time and cost of the project.

In situ microarray synthesis involves using microarray-based technologies already developed for gene expression in which a large number of oligos are synthesized on a microarray surface. These oligos are released off the surface and used as the pool for PCR-based assembly. The technology has potential for high cost savings and making gene synthesis very large scale. Its main limitations are that it is technically complex and is limited by the quality of the array-based oligos.

In PCR-based approaches, single bp mismatches or substitutions, insertions or deletions occur, and therefore the quality of the final product is influenced directly by the sequence accuracy of the starting oligos. Methods to remove mismatches include high-pressure liquid chromatography or polyacrylamide gel electrophoresis techniques to remove oligos with deletions or additions, and MutHLS protein-mediated removal of incorrect sequences from PCR amplification.

Solid-Phase-Based Approaches

Solid-phase assembly involves using a column containing a solid support to which double-stranded oligos (duplexes) are added sequentially, with intervening wash steps. It is conceptually analogous to oligo synthesis with the individual base monomers replaced by duplexed fragments of DNA. The main advantages of the solid-phase assembly approach are its simplicity (involving two fragments and three ends), ease of automation and applicability for any sequence.

In convergent assembly, a series of reactions are carried out involving two DNA fragments. In each step, the two fragments are ligated to one another and then purified. The advantage of this approach is that it uses a series of simple, reliable reactions and will work on nearly all sequences. The main limitation is the cost and time required, including significant bioinformatic inputs.

The bioinformatic expertise required for convergent assembly involves decomposing the target DNA construct into oligos with each fragment having ends that will ligate with the ends of other fragments. The oligo design must also be optimized for synthesis. The oligos must then be ordered to properly for convergent synthesis of the larger DNA construct.

All gene-synthesis technologies have error rates, and error removal is important. Going from oligos to cloned DNA fragments creates an error rate of about one in 300 (one base wrong in 300 base sequence). The best synthesis approaches have an overall error rate (including both the inherent oligo and the oligo to cloned DNA error rates) of about one in 500.

MICROFLUIDIC TECHNOLOGIES

Microfluidic technologies, including DNA microarrays and lab-on-a-chip, play key roles in DNA synthesis and sequencing. This is shown in the table below.

Microfluidic platforms reduce the size of an instrument and, consequently, reduce the consumption of reagents as well as allow for a high-throughput, massively parallel operation.

TABLE 16

IMPORTANCE OF MICROFLUIDICS TECHNOLOGIES IN SYNTHETIC BIOLOGY

Technology	Importance in Synthetic Biology
DNA microarrays	In situ microarray DNA synthesis is leading next-generation gene-synthesis technology
Lab-on-a-chip	Microfluidics is a critical component of all next-generation DNA-sequencing technology platforms

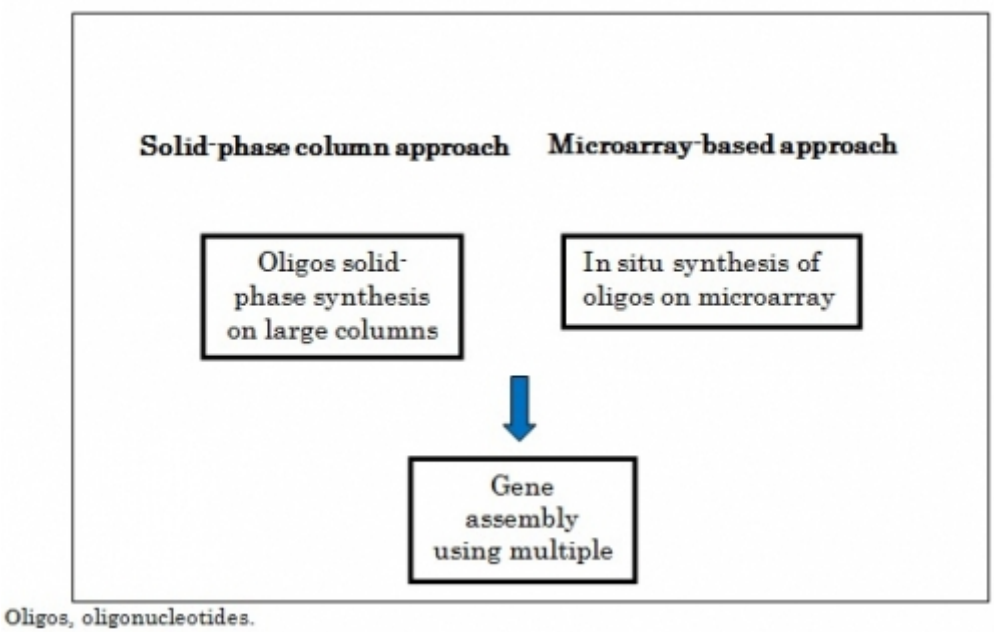
Source: BCC Research

DNA Microarrays

Microarrays play an important role in DNA synthesis, as is seen by the two general approaches in the figure below.

FIGURE 5

MICROARRAYS IN DNA SYNTHESIS



Source: BCC Research

The first approach is still widely used and employs solid-phase columns containing beads to which nucleotides are successively added to synthesize the oligo. The second approach, in situ synthesis on microarrays, is rapidly emerging. This approach adds nucleotides to the surface of DNA microarrays to synthesize the oligo. The advantages of this second approach are massively parallel synthesis of oligos and reduced consumption of synthesis reagents.

In a pioneering publication,[1] Quan et al. describe a high-throughput synthesis of long DNA molecules (e.g., synthetic genes) using a DNA microarray. The microarray contains thousands of short DNA molecules that were amplified and assembled enzymatically on the chip itself. This technology addresses a key bottleneck in synthetic biology today: the time and expense of synthesizing long genetic sequences.

NEXT-GENERATION SEQUENCING TECHNOLOGIES

DNA sequencing is the process of determining the precise order of nucleotides within a DNA molecule.

[1] Quan et al., Parallel on-chip gene synthesis and application to optimization of protein expression, *Nature Biotechnol.* 2011, 29, 449–52.

DNA sequencing is important in synthetic biology for several reasons. First, in oligonucleotide and gene synthesis, the synthesized DNA molecules need to undergo DNA sequencing so that their sequences can be verified. Sequencing is the final step in the gene-synthesis workflow. Second, large-scale genome projects involving sequencing generate a large amount of information about naturally occurring organisms. Synthetic biologists use this information to design parts and devices. Third, DNA sequencing allows verification of the sequence of novel constructs. For projects where the devices are hosted in bacteria, rapid evolution in these organisms can introduce mutations within constructs. This places a premium on rapid, low-cost methods of sequencing.

For creating production organisms in synthetic biology, DNA sequencing is important in helping to find new genes, planning for the genetic improvement of the organism and validating the organism after it has been constructed to verify that it has the designed genetic composition.

Key factors for NGS in achieving these goals are speed, the amount of data produced and cost.

First launched in 2005, NGS platforms have higher throughput than Sanger sequencing, permitting millions or billions of DNAs to be sequenced in parallel.

The following table shows the various formats for NGS, along with the main companies behind each format.

TABLE 17

NEXT-GENERATION SEQUENCING TECHNOLOGIES, BY COMPANY

	Company			
Technology	**Illumina**	**Oxford Nanopore**	**Pacific Biosciences**	**Thermo Fisher Ion Torrent**
Amplification	Clonal	Single molecule	Single molecule	Clonal
Detection	Optical	Nanopore	Optical	Solid state
Chemistry	Sequencing by synthesis	Nanopore	Sequencing by synthesis	Sequencing by synthesis

Source: BCC Research

The various commercial NGS technology platforms can be differentiated based on the amplification, detection and chemistry methods used.

DNA Amplification can be either clonal (practiced by Illumina, Ion Torrent) or single-molecule detection per reaction, well or sensor (Pacific Biosciences and Oxford Nanopore).

Sequencing base calls are made either optically (Illumina, Pacific Biosciences) or nonoptically by either solid-state sensors (Ion Torrent) or by measuring the translocation of DNA through a nanopore sensor (Oxford Nanopore).

The DNA that is measured to produce sequencing data can either originate from a single DNA molecule (Oxford Nanopore) or be generated by polymerase- or ligase-driven sequencing-by-synthesis reaction (Illumina, Ion Torrent, Pacific Biosciences).

GENOME-EDITING TOOLS

Genome, or gene, editing is a technique used to insert, delete or otherwise modify DNA for the purpose of silencing, activating or modifying an organism's genetic makeup. Genome-editing technologies have made a large impact in life science research and agricultural applications as well as offering the potential to transform disease management.

The main platforms used for genome editing are shown in the table below.

TABLE 18

COMPARISON OF GENENOME-EDITING PLATFORMS

Parameter	Platform			
	ZFN	**TALEN**	**CRISPR/Cas9**	**MegaNuclease**
Recognition site	9 bp to 18 bp per ZFN monomer; 18 bp to 36 bp per ZFN pair	14 bp to 20 bp per TALEN monomer; 28 bp to 40 bp per TALEN pair	22 bp to 44 bp	14 bp to 40 bp
DNA targeting	Triplet confined ZFPs	Single base recognition TALEN proteins	sgRNA	MegaNuclease
Off-target effects	Low	Low	Moderate	Low
Engineering ease	Difficult	Moderate	Easy	Difficult
Multiplexing	Low	Low	High	Low
Delivery ease	Easy	Easy for ex vivo, difficult for in vivo	Easy for ex vivo, moderate for in vivo	Easy
Targeting constraints	Non-G rich sequences	Sequences usually must start with a T	Sequences must start with a PAM element	Difficult to target novel sequences

bp, base pair; CRISPR, cluttered regularly interspaced short palindromic repeats; PAM, protospacer adjacent motif; sgRNA, single guide RNA; TALEN, transcription activator-like effector nuclease; ZFP zinc finger protein; ZFN, zinc finger nuclease.

Source: BCC Research

The four main genome-editing platforms include zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), CRISPR/Cas9 and MegaNuclease. Three platforms, ZFN, TALEN and MegaNuclease, target DNA via protein-DNA interactions. CRISPR/Cas9 targets DNA via bp matching of the guide RNA with the target DNA.

ZFNs are artificial DNA-binding proteins that can target and cleave specific parts of the genome for editing. ZFNs are composed of a nuclease domain (derived from a restriction enzyme) and a DNA-binding domain (mediated by zinc fingers). The ZFN recognition site is 9 bp to 18 bp, depending on the ZFN monomer used.

TALENs are artificial proteins that combine a nuclease (DNA-cleaving) domain with a DNA-binding domain – called TALE or MegaTAL – that is derived from the plant pathogenic bacterium *Xanthomonas*. The recognition site is 14 bp to 20 bp depending on the TALEN monomer used.

CRISPR/Cas9 combines a DNA recognition component, small-guide RNA with a DNA cleavage protein, CRISPR-associated protein (Cas9). The recognition site is 22 bp in length.

MegaNuclease platforms use one protein that has both a DNA-targeting and DNA-cleaving function.

Each of the four genome-editing platforms can recognize up to about 40 bp DNA. The main CRISPR/Cas9 platform can recognize up to 22 bp DNA, but by double nicking or Cas9-FokI fusion, this is increased to up to 44 bp.

For these technologies, the main differences as shown in the table above include the off-target effects, ease of delivery, multiplexing and ease of engineering.

Off-target modifications are important particularly in medical applications as these can cause oncogenic mutations and low-level off-target mutagenesis can result in catastrophic toxicity after cell expansion. ZFN, TALEN and MegaNuclease are safer in this regard because of their protein–DNA interaction mechanism. CRISPR/Cas9 may have higher off-target effects due to its Watson–Crick base-pairing mechanism.

Because of this potential concern for CRISPR/Cas9, efforts are ongoing to reduce the extent of any off-target activity. Strategies include: substituting the normal double-strand break with two separate single-strand breaks; conjugating the catalytically inactive Cas9 to RokI nuclease domain; and lowering the Cas9 concentration.

Also in clinical applications, effective delivery of the editing system to target cells is a key objective. Delivery in clinical applications is complicated by any off-target cleavage and immunogenicity caused by the delivery vectors or gene-editing tools used.

ZFN (2 kb) and MegaNuclease (0.8 kb to 0.9 kb) are smaller in size and thus more suitable for all types of delivery. TALEN (5.6 kb) and CRISPR (4 kb) are too large for Adeno-associated virus (AAV) delivery, making them less suitable for in vivo delivery.

CRISPR/Cas9 is the most easily engineered platform, making it a widely adopted choice for nonclinical applications in research or agriculture. This is because standard cloning procedures and oligo synthesis is used. CRISPR/Cas9 platforms can be very attractive for

clinical applications if their deficiencies (mainly off-target toxicity) can be satisfactorily addressed.

ZFN, TALEN and MegaNuclease are more difficult to engineer. ZFN and MegaNuclease may require substantial protein engineering. TALEN requires more complex molecular cloning approaches.

Despite their difficulty in engineering, ZFN and TALEN do have high specificity and activity when an optimized candidate is obtained, making them promising platforms for clinical applications.

The advantages and limitations of the main three genome-editing technologies are summarized in the table below.

TABLE 19

GENOME-EDITING TECHNOLOGIES: ADVANTAGES AND LIMITATIONS

Technology	Advantages	Limitations
ZFN	Recognizes longer DNA sequences	Off-target effects; engineering difficult; difficult to multiplex
TALEN	Wide targeting range; easy to design; recognizes longer DNA sequences	Difficult to multiplex; engineering moderately difficult
CRISPR/Cas9	Ease of design and construction; ready multiplexing	Target sites may be limited

CRISPR, cluttered regularly interspaced short palindromic repeats; TALEN, transcription activator-like effector nuclease; ZFN, zinc finger nuclease.

Source: BCC Research

ZFN can recognize longer DNA sequences by adding more zinc finger protein domains to the construct.

Limitations of ZFNs include off-target effects and difficulty in construction and multiplexing.

TALEN systems can target most DNA sequencing, including shorter sequences such as enhancers and microRNA coding region. TALEN can recognize long DNA sequences, giving it a high specificity. TALENs are easy to design because there is an exact relationship between the amino acid pairs and the nucleotides.

Construction of the DNA segments encoding TALEN arrays is time consuming, in part because these arrays have approximately 20 amino acid pairs. They can also recombine with each other with the cell.

A second limitation of TALEN is that multiplexing is difficult because two pairs are required and mismatches can occur, which in turn magnify off-target effects.

A key advantage of the CRISPR/Cas9 system is its ease of design and preparation. The Cas9 is the same and the short-guide DNA sequence is easily prepared by cloning in a vector that encodes the RNA fragment.

Using a single-guide RNA for DNA sequence recognition allows for constructing vectors with multiple-guide RNAs, permitting multiplexed gene targeting. This is a key advantage of CRISPR/Cas9.

In CRISPR/Cas9 systems, there is a requirement of protospacer adjacent motif sequences (5'-NGG-3'/5'-NAG-3') at the end of the guide RNA sequence. There is also a need for a guanine at the 5' end because the RNA polymerase III transcription event is done with a U6 promoter. These requirements somewhat limit the target sites.

GENE DRIVES

Gene drives work by biasing inheritance so that the ability of a genetic element to be passed on from parent to its offspring via sexual reproduction is increased. The end result of a gene drive is a preferential increase in a specific genotype, and therefore a specific phenotype, among a population.

From a technical standpoint, the two key elements of a gene drive are (1) a silenced or engineered genetic trait and (2) a way to drive the modified genetic element through a population via sexual reproduction. The first element includes gene silencing or modifying the genome to allow a trait to be expressed.

Driving genetic elements include transposable element or homing endonucleases.

CRISPR/Cas9 plays an important role in creating gene drives.

As of late 2016, most research on gene drives has focused on insects, with some on yeast and mice. This work has demonstrated that gene drives built with CRISPR/Cas9 tools are able to "drive" a specific gene through close to 100% of a population.

How well a gene drive works is determined, in part, by the cell type and species. More research is needed to optimize gene-drive approaches and to study the effect of environmental conditions and diversity of organisms.

Gene-drive-modified organisms have several potential market applications. These are shown in the table below.

TABLE 20

POTENTIAL MARKET APPLICATIONS FOR GENE-DRIVE- MODIFIED ORGANISMS

Market	Applications
Basic research	Modified model organisms for study of gene drives, disease mechanisms, species biology
Agriculture	Modify organisms that harm or pass on crop diseases; reduce prevalence of weeds that compete with cultivated crops
Public health	Control or change organisms that are threats to human health
Ecosystem health	Control or change organisms that are harmful to ecosystems; change organisms that are threatened or endangered

Source: BCC Research

The main market for gene-drive-modified organisms during the next five years is expected to be the research market. Other applications will take longer to commercialize due to several factors. One, gene-drive organisms will be subjected to extensive field trials to determine their ecological effect. Two, local and national regulatory authorities will have input on the eventual commercialization of gene-drive organisms. Three, the public will also need to be supportive of these technologies before they will gain widespread acceptance. Four, gene-drive technology is multidisciplinary, making it more challenging to develop and commercialize. The main fields included in this technology are synthetic biology, molecular-biology, genome editing, population genetics, evolutionary biology and ecology.

BIOINFORMATICS TECHNOLOGIES

Bioinformatics technology is important in many areas of synthetic biology, and particularly for gene synthesis. The table below shows two software platforms that are essential for the gene-synthesis process. Gene-design software is used to optimize how well the synthesized gene will express its protein product. Such software is especially important when the gene is to be used in a foreign, or heterologous, cell expression system. In that case, because the foreign cell system will have a different DNA codon (nucleotide triplet) preference for many amino acids, optimization of the gene DNA sequence is critical to achieving good expression levels.

TABLE 21

SYNTHETIC-BIOLOGY BIOINFORMATICS TECHNOLOGIES

Technology	Description	Significance
Comparative genomics	Used to determine select agents by gene-synthesis companies	Important for comparing a submitted sequence against list of harmful agents
Gene design	Optimizes protein-expression factors such as codon usage and mRNA secondary structure	Software is critical for optimizing protein expression in heterologous systems
Programming synthetic genomes	Allows design of novel genomes	Convert human-readable instructions to software language readable by a DNA synthesizer

mRNA, messenger RNA.

Source: BCC Research

Comparative genomics software is important for screening incoming gene orders against a list of harmful agents (select agents) that could be used as bioweapons. The submitted gene sequence should not match the sequence of a select agent.

In addition to gene synthesis, bioinformatics is critical technology for genomic and proteomic analysis that underpins many synthetic-biology applications. For example, gene-expression analysis software is a critical tool for understanding how well a heterologous protein-expression system is working. Bioinformatic tools are essential to operate NGS platforms.

Bioinformatics is a general tool of modern biotechnology that underlies much of the genomic and proteomic discoveries that are used in synthetic biology.

BIOLOGIC COMPONENTS AND INTEGRATED SYSTEMS TECHNOLOGIES

Synthetic biologic components and biologic integrated systems rely on synthetic DNA as the fundamental molecular component. DNA is composed of the nucleotides adenine (A), thymidine (T), cytosine (C) and guanine (G).

TABLE 22

NUCLEIC ACIDS, GENES AND GENOMES

Component	Structure	Biologic Function
DNA	Double-helix polymer with bases A, T, C and G	Core molecular polymer for synthetic biology
Gene	mRNA coding sequence, control regions	Encodes one or more proteins
Genome	Complete set of genes for an organism	Encodes the protein repertoire of the organism
Cell	Contains the genome and associated structures for expressing proteins	Stores and passes on genetic information; produces energy for the organism

A, adenine; C, cytosine; G, guanine; mRNA, messenger RNA; T, thymidine.

Source: BCC Research

dsDNA of various lengths and complexity forms the base building blocks for highly engineered biologic parts and systems.

The hierarchy of components of synthetic biology systems increases in complexity in moving from DNA to genes to genomes, chromosomes and finally, cells.

A gene is the DNA sequence that codes for a given messenger RNA (mRNA) sequence and subsequently, protein amino acid sequence. Besides the mRNA coding region, a gene also contains control sequences (i.e., promoters and stop signals) to aid in its transcription.

A genome consists of the complete set of genes of an organism. Genomes consist of separate chromosomes, the number of which varies by species.

Cells contain the organism’s genome and associated organelles and structures for expressing protein products and producing energy via specific metabolic pathways to maintain the organism.

SYNTHETIC DNA

Synthetic DNA consists of oligos, DNA constructs and genes. Each of these DNA types plays an important role in synthetic biology.

TABLE 23

SYNTHETIC DNA

Synthetic DNA Type	Length	Strands
Oligos	Short	Single stranded
DNA constructs	Short-long	Single stranded
Genes	Long	Double stranded

oligos, oligonucleotide.

Source: BCC Research

Oligos are short strands of DNA, while genes are much longer in length.

DNA constructs, also known as BioBricks, are DNA parts, usually longer than an oligo but shorter than a gene, which possess some sort of functionality, such as promoter or terminator. DNA constructs are made up of the DNA encoding for the protein or regulatory device, as well as two flanking sequences called “cut sites.” These cut sites are recognized by restriction enzymes.

DNA constructs introduce standardization and modularity, making them important in synthetic biology for assembly into more complex genetic circuits. There is a trend toward longer constructs that incorporate multiple separate functional DNA parts; this eliminates the need for modularity in assembly. These longer fragments can be joined together rapidly and easily leaving no scar. As the cost of DNA synthesis continues to fall, longer DNA constructs should become more widely used.

Synthetic genes have important functions as core parts for more complex synthetic biology integrated systems and as a molecular-biology tool (see table below).

TABLE 24

SYNTHETIC GENES AS MOLECULAR-BIOLOGY TOOL

Feature	Importance to Molecular Biology
Unique source of DNA	May be the only accessible source for the desired DNA
Sequence can be deduced and designed in silico	Frees researchers from experimental-derived sequences
Can be easily mutated at defined positions	Useful for generating protein variants; improved expression levels in host cells or model organisms; allows for construction of complex gene constructs

Source: BCC Research

Synthetic genes are the only viable source of DNA in cases where the natural DNA is not available or does not exist for the desired sequence.

Synthetic genes can be designed entirely from scratch on the computer and they are easily modified and engineered in silico (i.e. on the computer). Thus, this allows

researchers much more freedom in the design of such genes than naturally occurring genes. This then makes synthetic genes very useful for protein engineering or improves their expression in new host cells. Re-engineering can occur in the coding region or regulatory regions (protein initiation, ribosome binding sites, promoters, etc.) of the DNA. Codons (three-base sequences that code for a specific amino acid) can be optimized for a specific host cell or model organism. These design abilities also allow for construction of related but different constructs that have variability at specific regions of interest. Combining these factors provides a high degree of flexibility to design target sequences while minimizing intermediate steps (e.g., cloning and recombination) requiring conventional methods.

The design of a gene sequence in silico is done using bioinformatic technologies. The design objective is (usually) to optimize elements that affect expression of a target protein. These elements include formation of secondary structures, which could prematurely stop protein synthesis, sequences that code for regulatory elements (e.g., signal peptides or introns) and codon preferences of the host organism.

Matching codons to the coding preference of the host organism is especially important. DNA uses four different nucleotides – G, A, T and C – as code for amino acids. Each amino acid is coded by a codon. Therefore, there are 64 (4^3) codon choices possible for coding the 20 different nucleic acids used for protein synthesis. For any given amino acid, there are up to six different codons available. A gene coding for a particular protein can therefore be quite variable in its codon composition.

There is a high amount of diversity among species in the use of alternative codon sequences. For example, plants prefer GC-rich sequences, while animals prefer AT-rich sequences. Bacterial strains often have different codon preferences. An example of these preferences is the bacterium *Escherichia coli* K12, which prefers the codon AAA (versus AAG) for the amino acid lysine. In this bacterium, three-quarters of the codons for lysine are AAA. This is distinctly different from the plant *Zea mays* (maize), which prefers AAG for lysine over 72% of the time.

The importance of codon preferences is the level of protein expression when a foreign gene is inserted into a host system. If the foreign gene uses codons that are not preferred by the host system, protein expression is poor. The reason for this is a bottleneck in a key intermediary in protein synthesis – transfer RNAs (tRNAs). The host system has only a limited inventory of tRNAs that can transport certain amino acids during protein synthesis. When a rarely used codon is introduced into this system, the available tRNAs corresponding to this codon rapidly delete, and either translation of the foreign gene slows down or the wrong amino acids incorporate into the growing peptide chain.

For this reason, adapting codons to the host system is a key design feature for synthetic genes. Codons in the foreign gene that have low preference by the host system must be replaced by codons with a high preference. This should be done without changing the amino acid sequence of the desired protein.

The advantages of synthetic genes provide a basis for competing with PCR cloning molecular-biology methods, as shown in table below.

TABLE 25

SYNTHETIC GENES VERSUS PCR CLONING

Gene Characteristics	PCR Cloning	Synthetic Genes
Translation from one species to another	Not optimized	Optimized
Ability to change DNA sequence	Limited	Unlimited
Presence of mutations or SNPs in DNA sequence	Common	Rare
Length of DNA construct	Short	Long

PCR, polymerase chain reaction; SNP, single nucleotide polymorphism.

Source: BCC Research

In PCR cloning, a DNA fragment is extracted from one species (e.g., mammal) and is inserted into the genome of another species (e.g., bacteria or yeast). Often, the host species has difficulty translating the foreign DNA code, resulting in reduced production efficiency. The use of synthetic genes allows revision of the foreign DNA code so that it can be easily translated by the host organism. The core genetic message is unaltered, so the identical protein is produced at much higher efficiency.

A second advantage of synthetic genes over PCR cloning is that it allows an unlimited number of protein variants to be created, thus introducing the ability to improve protein products. In the production of synthetic genes, each base can be easily changed, which means that each amino acid of a particular protein can be altered. This allows researchers to cost effectively and rapidly test multiple variants of a gene to find one that meets the desired objective. This feature is especially useful for production of industrial enzymes and in drug and vaccine discovery.

This ability to synthesize completely novel DNA sequences can improve the laboratory workflow. Many of the labor-intensive steps in conventional molecular biology (e.g., preparation of a complementary DNA library) can be bypassed, and large, engineered DNA fragments can be ordered from gene supply firms.

PCR products may contain mutations or single nucleotide polymorphisms that can cause issues in experiments. Synthetic genes can be easily quality controlled for precise, unmutated genes. Based on data published by BD Biosciences, PCR success rates decline as the gene becomes longer: 90% success rate for 200 bp genes versus only 60% for genes greater than 2,250 bp. In contrast, the success rate for gene synthesis does not depend on the length of the gene. Thus, longer-length genes can be made more rapidly and with higher success probability with synthetic approaches compared with PCR cloning approaches.

A limitation of PCR cloning is that some gene sequences are too lengthy to synthesize. This is not a limitation with synthetic-gene approaches, allowing researchers access to all genes, regardless of their length. The NIH Mammalian Genome Collection used synthetic-gene technologies for several thousand of the most difficult and lengthy genes, which were not possible to make using PCR cloning.

Synthetic genes are particularly useful when any of the following conditions occur. The protein sequence is known but no DNA sequence information is available. The desired gene contains unusual features (i.e., rare species, expressed in rare tissue, or rare splicing variant). The desired sequence needs to be changed (e.g., for codon optimization, domain swapping, insertion, deletion or multiposition mutation). The gene is from a rare species making samples difficult to obtain. A high expression level is desired.

A final consideration is the cost of cloning versus synthetic genes. For many projects, gene synthesis is less costly than conventional methods. In 2014, the cost for synthesizing gene-length DNA was less than $0.20 per bp. The cost for synthesizing short oligos was less than $0.10 per bp. This compares with cloning methods, which can cost up to $1.00 per bp. The cost of synthesis is declining rapidly, providing an even larger cost gap in the future.

Cloning requires skilled technicians who can work with tissue samples to isolate DNA. Synthetic genes allow research laboratories to skip these traditional molecular-biology steps and simply order a given DNA sequence from a gene vendor.

The adoption of synthetic genes as a replacement for cloning will occur as a function of the cost of synthetic genes and the learning curve of researchers in understanding the benefits and possibilities of using synthetic genes.

BIOBRICK PARTS

BioBrick parts (also known as DNA constructs) are pieces of RNA, DNA or amino acids that are or encode functional genetic elements or parts of proteins. Examples are described in the table below. BioBricks are promoted as an open-format, wiki-enabled registry at partsregistry.org. The registry is provided to all users as a source of standardized parts that perform specific functions such as those listed in the table. Parts are designed to be cloned into standard plasmid backbones.

TABLE 26

DNA CONSTRUCTS

Part	Function
Promoter sequences	Recruits transcriptional machinery, which leads to transcription of DNA into mRNA
Terminator sequences	RNA sequence at the end of a gene or operon mRNA that causes transcription to stop
Ribosome binding sites	An RNA sequence found in mRNA to which ribosomes bind and initiate protein synthesis
Protein domains	Portions of proteins that are cloned with other proteins to make up a protein sequence. Protein domains can change a protein’s location, alter its degradation rate, target the protein for cleavage and enable it to be purified
Protein coding sequences	Codes the amino acid sequence of a specific protein or protein domain

Translational units	A ribosome binding site and a protein coding sequence
DNA parts	Add functionality to the DNA itself, and include cloning sites, scars, primer binding sites, spacers, recombination sites, conjugative transfer elements, transposons, origami and aptamers
Plasmid backbones	A plasmid sequence including the BioBrick prefix, replication origin, antibiotic resistance marker and BioBrick suffix

mRNA, messenger RNA.

Source: BCC Research; partsregistry.org

Key requirements of a standardized part are that it must be able to send and receive standard biochemical signals and be cut and pasted into a linear sequence.

Part types available include systems, devices, parts, chassis and vectors. Devices include promoters, reporters, inverters, protein generators, receivers and senders, and measurement devices.

The parts offered enable a wide variety of functions, including biosynthesis, cell to cell signaling and quorum sensing, cell death, coliroid (parts that enable taking a bacterial photograph), conjugation, motility and chemotaxis, odor production and sensing, DNA recombination and viral vectors.

Chassis available include *E. coli*, *S. cerevisiae*, *Bacillus subtilis*, bacteriophage T7 and cell-free systems. Synthetic biologists are expanding this list to include organisms that can survive and produce in harsh manufacturing conditions, such as high temperatures, or that can utilize carbon feed sources other than sugars, such as methane.

Cell-free systems use only the essential parts of the cellular machinery, such as the enzymes needed for energy and cofactor regeneration and for protein syntheses. Cell-free systems are more flexible in what manufacturing conditions can be used and can be more readily optimized for manufacturing without having to be concerned about maintaining healthy cells.

To illustrate the use of these parts in synthetic biology, we discuss synthetic promoters and reporters in the figure below.

Promoters are DNA sequences that are located upstream of the gene-coding sequence. The promoter is a binding site for proteins called transcription factors (TFs). RNA polymerase binds TFs as the initial step in transcription of the gene itself. Thus, TFs are important controls for gene expression.

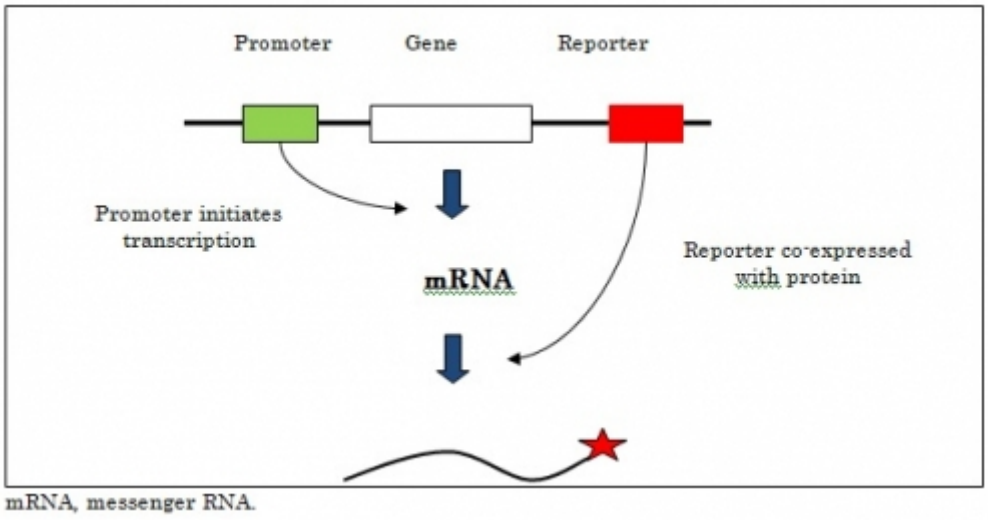
Reporters are genes, such as beta-galactosidase or fluorescence proteins that provide a measurable signal when transcribed. Reporters can be attached to other gene sequences to provide a way to know if and when these sequences are being transcribed.

Synthetic promoters and reporters are used to model genetic circuits in synthetic biology. Prior to building a specific biologic system, the synthetic biologist must know how each component of the mechanism or gene circuit will work. Synthetic promoters and reporters are specifically designed and selected and therefore make gene circuit modeling much easier.

The second way in which promoters and reporters are useful occurs when a wild-type promoter or reporter is not sufficient or lacks a necessary property for the cellular mechanism to work. An example of this is when a transient signal needs to be detected using a green fluorescent protein (GFP) reporter. Ordinarily, GFP does not degrade immediately after it is produced, so it is useless for detecting transient signals of a biologic system. However, a synthetic GFP reporter that degrades quickly would be useful. The same holds true for reporters that are more active at lower or higher than normal temperatures.

FIGURE 6

ROLE OF PROMOTERS AND REPORTERS IN SYNTHETIC-BIOLOGY SYSTEMS



Source: BCC Research

Reporters and promoters can be used to design gene switches and circuits for more precise control of gene-expression levels. This can be a useful tool in a number of applications, including gene therapy, tissue engineering, functional genomics, production of therapeutic proteins and engineering stem cells.

Gene regulatory switches have also been developed that combine repressor proteins with RNA interference technology to achieve very high levels of gene inhibition. These switches can be used to discover potential drug targets by identifying mediators of cellular processes. The regulatory switch is used to control the level of expression of candidate proteins to evaluate the resulting phenotype effect on cell lines.

MINIMAL GENOMES AND CHASSIS ORGANISMS

A minimal genome consists of the minimum set of genes required for survival in a particular environment and for performing a specific function (see table below). Organisms with minimal genomes are also referred to as “chassis organisms” since their genome can serve as the foundation for adding additional synthetic parts for

TABLE 27

ATTRIBUTES OF A MINIMAL GENOME

Attribute	Advantages
Survives in a specific environment	Metabolic activity of cell is conserved to survival functions, freeing up energy for design functions
Performs a specific function	Cell system can focus primarily on a specific function such as protein production
Improves safety profile	Higher-quality biologic drugs
Unwanted proteins are absent	Makes transfection and protein purification easier and less costly

Source: BCC Research

The construction of the minimal genome (including the number of genes and specific types of genes) varies based on the organism, environment and specific purpose.

Possessing a minimal genome allows a cell to perform only the necessary functions required for survival and for the specific function. This means that metabolic activity of the cell is not expended on unnecessary tasks that require the cell's energy and chemical resources. The result is a much more efficient cell for producing, for example, a biologic product. A second advantage of using a minimal genome for biologic drug production is increased safety because some genetic elements such as gene swapping are removed, therefore making it less likely that the coding region for the drug can be altered.

The current bacterial host systems can be made more efficient by adopting minimal genomes. First, a bacterial genome has many unnecessary genes that require metabolic energy to reproduce each time the cell divides and to produce unneeded proteins. These include condition-responsive genes for adapting to the natural environment including temperature, stress or food. Bacteria that are used in cellular production factories have a controlled environment within the fermentation tank, reducing the need for these condition-responsive genes.

Second, many proteins in a normal bacterium negatively affect the production or purification of a desired protein. For example, some proteins can interfere with the introduction of a plasmid into *E. coli* bacteria and its maintenance within the cell after transfection. In addition, purification of a recombinant protein may be interfered with by naturally occurring proteins produced by the bacterial host cell. Also complicating purification, many bacterial strains produce toxins that need to be separated from the desired protein product. Some strains can produce proteins that may be close in size to the target protein, making separation even more difficult.

For these reasons, minimal genomes that do not produce these complicating proteins are desirable.

However simple it may seem to make deletions to a genome, creating a minimal genome is not a trivial task. It is difficult to make targeted deletions of specific regions of DNA, and even more difficult not to leave artifacts (inserted DNA or mutations) in the genome after making these changes. Artifacts are harmful because they can become regions for

unwanted recombination events that could remove genome regions or cause genome rearrangements. They can also become unwanted targets for other deletions where multiple deletions are performed, rendering the genome genetically unstable.

Professor Frederick Blattner of the University of Wisconsin–Madison provided the technical proof of principal for minimal genomes in 2006 (see Case Study below). Professor Blattner showed that by removing approximately 15% of *E. coli*'s genetic material, the new strain could produce a protein used in vaccines more efficiently than the standard strain. One of the genes removed in this experiment disabled the bacterium's ability to swim, which uses energy resources that are not necessary for producing proteins.

Since the smallest genomes of natural organisms contain only a few hundred genes, chassis organisms containing minimal genomes should have a few hundred genes. There are two general approaches to creating minimal genomes: synthesis from scratch, and deletion of nonessential genes and DNA from an organism's natural genome. Synthetic Genomics used the synthesis from scratch approach, with its synthesis of the first artificial minimal genome, Mycoplasma, in 2008. The second approach is followed by Scarab Genomics, with its minimal *E. coli* that has over 15% of its natural genome deleted (nonessential genes and DNA sequences).

Case Study: Minimal E. coli Genome

In 2006, Professor Frederick Blattner of the University of Wisconsin–Madison published research establishing that scientists could massively restructure an organism's genome and design it to perform specific functions. This represented a key achievement in synthetic biology by showing that massive genome restructuring could work. Blattner's group compared the genomes of different strains of the bacterium *E. coli* to assess which genes were required for survival. They removed those genes that were not essential for survival, which represented approximately 15% of the genomic DNA.

One potential application for this chassis organism is the production of biologics currently made in bacteria. Since the gene-swapping elements are removed from the bacterium, the DNA region coding for the drug is unlikely to be inadvertently mutated, providing a safety and efficiency advantage.

Chassis organisms with minimal genomes are an emerging molecular-biology tool. The main advantages include improved metabolism, growth in rich and minimal media, protein synthesis, transformation efficiency, genomic and plasmid stability, safety and ability to clone previously unclonable genes.

Despite the promise of minimal organisms, there is some question whether or not they will be used widely in industry. This is because natural organisms that display genetic and phenotypic heterogeneity are more robust and have more genetic variation.

Role of Directed Evolution in Designing Biologic Parts

Directed evolution is a technique for mutating DNA sequences to obtain desired features. Directed evolution can be used as a tool for designing better biologic parts, such as reporters or promoters, as well as finding new or improved genes.

Directed evolution works in a four-step process:

1. Mutate or scramble the DNA sequence.
2. Screen the changed sequences against a desired phenotype, and remove any cell that lacks the desired phenotype.
3. Amplify the surviving cells that display the desired phenotypes.
4. Repeat steps 1 through 3 of the process with the amplified cells.

Many cycles can be performed, resulting in a DNA sequence that may be changed significantly from the original and that will express the desired phenotype. Using this tool, biologic parts with very specific functions can be obtained.

ENABLED TECHNOLOGIES

The power of synthetic biology is that is a means to practice industrial biotechnology on a large scale. Synthetic biology enables a wide range of downstream products including pharmaceuticals, biofuels and chemicals. In this report, we choose to focus on existing and near-term enabled products, which are shown in the table below.

The technologies shown in this table are those included in our five-year market forecasts later in this report. The main technologies include new bio-based production processes for pharmaceuticals, chemicals and fuels, and discovery methods for new pharmaceuticals.

TABLE 28

ENABLED TECHNOLOGIES: KEY APPLICATION FIELDS

Technology	Near-Term Applications
Pharmaceuticals	New pathway to synthesize naturally occurring drugs and antibiotics; discovery of novel drugs; DNA vaccines
Biofuels	Ethanol, renewable diesel and gasoline, butanol
Chemicals	New manufacturing routes to produce biofuels, cosmetics, lubricants, food and agriculture products, polymers and surfactants
Agriculture	Novel crop plants, pest-control systems, genome-edited animals

Source: BCC Research

Opportunities for producing pharmaceuticals via synthetic biology include drugs that are currently available in limited quantities from natural sources (artemisinin), diabetes drugs (Januvia), antibiotics (cephalexin) and vaccines (influenza).

Biofuels include cellulosic ethanol, renewable diesel, renewable gasoline and butanol.

Chemicals include those used in biofuel production (e.g., enzymes), polymers, cosmetics, food and agriculture, lubricants and surfactants.

Agricultural technologies include biofuel feedstocks, crop plants, pest-control systems and genome-edited porcine and beef/dairy cattle.

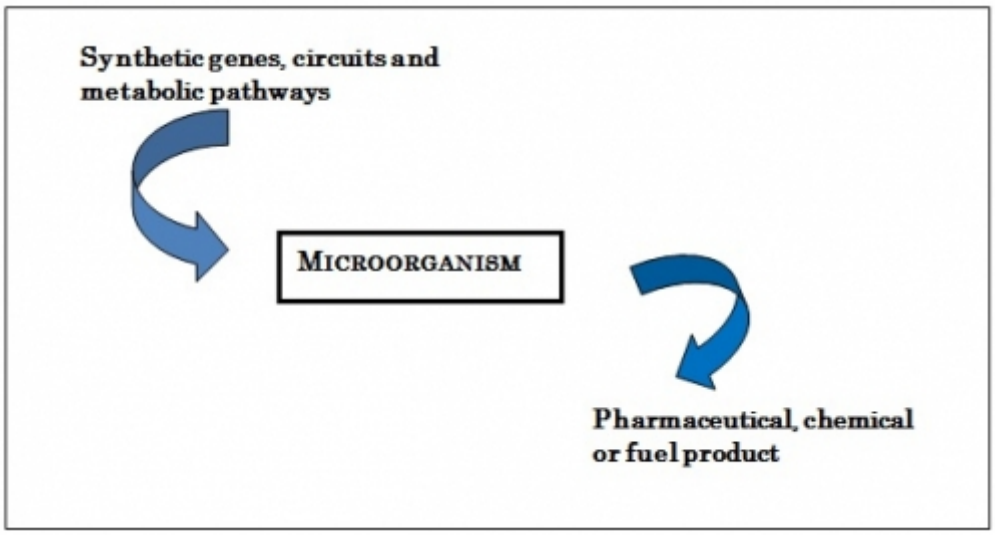
PATHWAY ENGINEERING

The key to synthetic-biology-enabled products is pathway engineering. Pathway engineering (also known as metabolic engineering) optimizes the genetic and regulatory processes within cells or microorganisms to increase the cell's ability to produce a given compound. Pathway engineering enables design of producer cells, which form the basis for cellular factories for producing pharmaceutical, fuel or chemical products (see figure below).

Cell factories use synthetic genes that have been designed on computers. These genes are then spliced into a microorganism's genome based on metabolic engineering principles.

FIGURE 7

HOW SYNTHETIC BIOLOGY CREATES ENABLED PRODUCTS



Source: BCC Research

During the mid-2000s, a pioneering synthetic project was undertaken to develop a process for synthetic artemisinin (used in malaria drugs). The metabolic pathway engineering design for this project involved expressing 12 genes simultaneously in yeast cells and

controlling their outputs to balance the pathway. Artemisinin represents an early application of synthetic biology to metabolic engineering, and it is illustrative of the power of this tool.

The table below shows several of the key genetic changes that were made using synthetic-biology approaches and the increase in efficiency that resulted.[2] The key aspects of the metabolic engineering, which differentiate it from genetic engineering or even enzyme engineering, are use of codon-optimized synthetic DNA, insertion of a heterologous yeast pathway and the redesign of the control of the metabolic pathway.

TABLE 29

METABOLIC ENGINEERING FOR ARTEMISINIC ACID

Metabolic Engineering Step	Improvement Achieved
Codon optimization of the *Artemisia annua* enzyme amorphadiene synthase, introduction into the high FPP producer yeast to convert FPP to amorphadiene	142X
Insertion of yeast mevalonate pathway	30X
Optimization of intragenic mRNA structures of the synthetic mevalonate operon	7X

FPP, farnesyl pyrophosphate; mRNA, messenger RNA.

Source: BCC Research; Ro et al. 20062

The result of the engineering was to combine metabolic pathways from bacteria, yeast and the plant *Artemisia annua* into an *S. cerevisiae* yeast genome that can synthesize large quantities of the active pharmaceutical ingredient for artemisinin. Overall efficiency improvement is nearly 200X. These dramatic results illustrate the potential that synthetic biology has for metabolic engineering.

The engineering of the final yeast producer cell involved three key synthetic biology steps:

1. Engineering of the farnesyl pyrophosphate (FPP) biosynthetic pathway to increase FPP production and decrease its use for sterols.

2. Introducing the amorphadiene synthase gene from *A. annua* into the high-FPP producer yeast cell to convert FPP to amorphadiene.

3. Cloning a novel cytochrome P450 that performs a three-step oxidation of amorphadiene to artemisinic acid from *A. annua* and expressing it in the amorphadiene producer cell.

[2] Ro et al., Production of the antimalarial drug precursor artemisinic acid in engineered yeast, *Nature*. 2006, 440, 940–43.

A second example of metabolic engineering is production of a synthetic analog of spider dragline silk protein (DP1B) in *Arabidopsis*. Spider silk is as strong as Kevlar but with 10 times the elasticity. Yang et al.[3] described a synthetic DP1B gene that produced the silk protein in a genetically modified plant at a concentration of 1.5% of total soluble protein in the plant cells. By specifically targeting certain regions of the cell, the DP1B productivity could be increased up to 7.8 times.

A third example involves work done by DuPont, Danisco (subsequently acquired by DuPont) and Tate & Lyle to re-engineer an *E. coli* bacterium with synthetic-genetic networks to produce propanediol, a key component of Sorona, a spandex-like fiber made by DuPont. A factory to produce this biomaterial was built in 2006. The companies made over 100 changes to *E. coli* to increase yields by the synthetically engineered bacterium from near zero to 150 grams per liter of propanediol.

The pathway engineering applications we have discussed thus far involve making changes to a single organism, such as *E. coli* or *Arabidopsis*. Many of the changes involve multiple steps or processes. Engineering all of these steps into a single organism can become complicated and presents a limitation to synthetic biology. Pathway engineering in microbial consortia may be a way to overcome this limitation and represents a frontier area of synthetic biology.

RESEARCH AND DEVELOPMENT APPLICATIONS

The availability of DNA sequence data and low-cost sources of synthetic genes is transforming the field of proteomics. In the past, a researcher studying, for example, a particular protein would need to isolate the gene for that protein, insert the gene into a bacterium and produce and isolate the protein. Using synthetic genes, the researcher only orders the gene from a gene-synthesis company and expresses that gene in a host organism. Using the synthetic gene, the researcher can avoid obtaining the entire gene from its natural source. The table below summarizes these applications.

TABLE 30

RESEARCH AND DEVELOPMENT APPLICATIONS FOR SYNTHETIC-BIOLOGY PRODUCTS

Application	Synthetic-Biology Products
Study of protein structure–function relationships	Synthetic genes, synthetic tissues
Proteomics	Synthetic genes, biologic parts, metabolic engineering
Directed evolution	Synthetic genes, biologic parts
Increased expression and yield of proteins	Synthetic genes, biologic circuits, metabolic engineering, minimal genomes

Source: BCC Research

[3] Yang et al., High yield recombinant silk–like protein production in transgenic plants through protein targeting, *Transgen. Res.* 2005, 14 (3), 313–24.

In proteomics, increased protein expression and yields will aid researchers doing structural biology and for those expressing difficult-to-express proteins. This will accelerate downstream research in a number of life sciences fields.

Optimizing protein expression and yield is an important goal of researchers. Adapting genes to expression in foreign, or heterologous, cells is also a desired objective. Being able to express proteins in high yield in heterologous systems is important for generating enough protein material for downstream experiments, such as structure–function studies. Synthetic-biology tools including synthetic genes, gene-variant libraries, gene-control circuits and metabolic engineering allow for optimized expression. One approach is to create systematically varied gene sets, measure protein-expression levels and select the genetic variation that is responsible for higher producing variants.

To meet this need, each of the leading gene-synthesis companies offers protein-expression optimization bioinformatic services for the best design of genes. Protein expression is a key factor by which gene-synthesis companies differentiate their products to the life sciences market.

Use of host organisms with minimal genomes can have a large impact on protein-expression efficiency, and this is another area where synthetic biology plays a key role. Eliminating nonessential genes from a genome improves its metabolism and genetic stability. Cells with minimal genomes (chassis organisms) also exhibit better transfection efficiency. These properties make chassis organisms a useful tool for molecular biologists.

BIOFUELS TECHNOLOGIES

OVERVIEW

Producing fuels via biologic processes involves three key choices: feedstock, final product(s), and the technology (e.g., microorganism type) for converting the feedstock to final product(s). Each of these choices is strategic and ultimately determines the competitive position of the company.

The table below summarizes these factors.

TABLE 31

ADVANCED BIOFUELS TYPES

	First Generation	Second Generation	Third Generation	Fourth Generation
Feedstock	Food crops	Lignocellulosic biomass, nonfood crops or bio oil	Algae	Genetically modified carbon-rich feedstock
Technology	Fermentation or transesterification	Anaerobic digestion and BTL	Gasification and Fischer–Tropsch process	BTL, CCS

End product	Esterized biodiesel	Biohydrocarbon	Biohydrocarbon or oilgae	Carbon-negative biofuel
Status	2000	2007	2020	R &D
Oil yield (U.S. gallons per acre)	20 to 85	20 to 630	1,500 to 5,000	R &D

BTL, biomass to liquid; CCS, carbon capture and sequestration; R &D, research and development.

Source: BCC Research

Next-generation technologies are focusing on using more efficient feedstocks, including jatropha seeds, palm oil and algae. The advantage is that there is no impact on food supplies and pricing and there is a much greater yield of oil per acre.

Jatropha and palm oil yield 202 U.S. gallons per acre and 635 U.S. gallons per acre, respectively, and these are much higher than first-generation feedstocks (20 U.S. gallons per acre to 85 U.S. gallons per acre). Algae yields are even higher, at 1,800 U.S. gallons per acre. For algae, much less land area is required for production, making it a very attractive option.

Fourth-generation biofuels use genetically modified carbon-rich feedstock to produce energy-rich hydrocarbons such as branched chain higher alcohols. These technologies use a carbon negative process (carbon capture and sequestration processes), so that more carbon is removed from the atmosphere than is released. These technologies are in the research and development stage and will compete with second-generation fuels. Fourth-generation biofuels are projected to have energy content similar to fossil fuels, with physical and chemical properties similar to gasoline. Therefore, they may be able to replace fossil fuels without any modifications.

Commercialization of fourth-generation biofuels will depend on how well the synthetic-biology tools advance the technology innovation and how well they can compete with second-generation biofuels.

The advanced biofuels market is at the stage of precommercial production technology development. Key factors in its future development are access to capital, access to sufficient feedstocks and building an efficient delivery infrastructure.

FIRST- AND SECOND-GENERATION BIOFUEL TECHNOLOGIES

As seen in the discussion above, the vast majority of biofuels produced today are first generation. However, second-generation fuels produced from cellulosic biomass are rapidly emerging and synthetic biology plays a key role in these technologies. Second-generation biofuels are produced via a multistep process: biomass pretreatment, conversion to sugars, followed by fermenting sugars to fuels.

The table below illustrates the primary limitations of first-generation biofuels. First-generation fuels use food crops as feedstocks. Feedstocks are derived from sugars, grains or seeds, and the conversion process uses only a specific, edible portion of the

above-ground biomass of the plant. Since feedstocks are optimized for food and not energy, fuel demand competes with food demand, creating market imbalances. In contrast, second-generation fuels have no impact on the food chain because neither grains nor other food sources are used as feedstocks.

TABLE 32

FIRST--AND SECOND-GENERATION BIOFUELS COMPARED

Factor	First Generation	Second Generation
Feedstocks	Food (C-6)	Cellulosic (C-5, C-6, lignin), nonfood
Greenhouse gas benefits	Modest	High
Transportation infrastructure	Compatible with existing	Infrastructure must be developed
Feedstock cost	High	Low
Proportion of plant mass converted to fuel	Low	High
Energy and environmental benefits	Low	High
Capital intensity	Low	High
Current production costs	Moderate	Moderate–high

Source: BCC Research

First-generation fuels provide relatively small greenhouse gas benefits (with the exception of sugarcane ethanol) and are relatively high cost due to the feedstock costs (again, with the exception of sugarcane ethanol in Brazil). Conversion of the feedstock plant mass to energy is low (i.e., most of the plant mass is not converted to fuel).

Advantages of first-generation fuels include compatibility with existing transportation infrastructure and low capital intensity and production costs (due to the ease of converting C-6 sugars to fuels).

Second-generation fuels are attractive because they use nonfood feedstocks – cellulosic biomass. With cellulosic biomass, a larger fraction of the plant mass can be used for fuel, and the plants can be optimized for energy content and not food factors. Feedstock costs are lower because cellulosic crops can be cultivated on poor-quality land, with fewer fertilizers. Many cellulosic technologies have the capability to switch among feedstocks with only minor modifications. This gives greater flexibility for plants in selecting feedstock mixes over time for any given plant. In addition, using nonedible feedstocks is a key factor in helping to stabilize the price fluctuations of biofuel feedstocks in advanced-generation fuels.

Because there is higher biomass usability per unit of land area, there are more energy and environment benefits for advanced-generation fuels.

The key technical difference between first- and second-generation feedstocks is in the chemical composition. Advanced-generation feedstocks consist of cellulose, while

first-generation feedstocks are composed of C-6 carbons that are more easily converted to sugar.

In the following sections, we will further describe and compare these two feedstock types (crop and cellulosic), as well as more advanced feedstocks (algae and carbon dioxide [CO_2]).

CROP FEEDSTOCKS

Feedstocks can be ranked on their energy balance (ratio of energy output to energy required for production). The table below shows the energy balances of the main producing crop feedstocks used for biofuel production. The data in the table show that sugar cane has the highest energy balance. An energy balance of greater than 1 means that a feedstock generates more energy than was required to grow the crop, and thus the higher the energy balance the more efficient the conversion to fuel.

TABLE 33

ENERGY BALANCE OF SELECTED FIRST-GENERATION BIOFUEL FEEDSTOCKS

Feedstock	Energy Balance
Sugar cane	4.5 to 8.0
Rapeseed	3.5
Sugar beet	1.3 to 2.1
Wheat	1.0 to 1.5
Maize	1.0 to 1.4
Corn	1.2

Source: BCC Research; U.S. Department of Energy (IEA)

The feedstocks listed in this table are used to produce first-generation biofuels. These feedstocks are used for food production as well as biofuel production.

Other feedstocks are not suitable for food, but are being developed for fuel production. These feedstocks include cellulosic biomass, algae and CO_2. Fuels produced from these feedstocks represent advanced next-generation biofuels.

CELLULOSIC FEEDSTOCKS

Cellulosic biomass consists mainly of cellulose (6-carbon sugars), hemicelluloses (5-carbon sugars), lignin (aromatics) and others (see table below).

TABLE 34

APPROXIMATE COMPOSITION OF CELLULOSIC BIOMASS
(%)

Component	Percent
Cellulose	45
Hemicellulose	28
Lignin	20
Other	7
Total	100

Source: BCC Research

The biomass origin can be either the nonedible residues of food crop production (e.g., rice husks or corn stalks) or nonedible whole-plant biomass (e.g., trees or grasses grown for energy purposes). Because of its composition, the production process for converting cellulosic biomass into a biofuel is more technically challenging compared with first-generation fuels. The main challenge is the hydrolysis of cellulose to convert all components (hemicelluloses, cellulose and lignin) into simple 6-carbon sugars ready for fermentation. The biomass must first be pretreated to make the cellulose accessible to hydrolytic treatment. Pretreatment may include chemical, physical or enzymatic methods. After pretreatment, a second challenge is to convert 5-carbon sugars to 6-carbon sugars so they can be fermented by yeast. These additional steps add to the capital and processing costs.

Synthetic-biology approaches can minimize or eliminate one or both of these steps, saving considerably on costs. Using ethanol as an example, one synthetic-biology approach is to engineer cellulose-degrading enzymes into an ethanol-producing organism. This can be done using natural celluloytic organisms or by engineering celluloytic enzymes into a foreign microorganism.

A second challenge after breaking down the cellulose into sugars (mix of 5- and 6-carbon sugars) is how to convert the 5-carbon sugars into ethanol. Conventional ethanol yeast organisms use 6-, not 5-carbon sugars and thus are not suitable for this step. The table below summarizes the various synthetic-biology strategies for addressing this problem.

TABLE 35

SYNTHETIC-BIOLOGY STRATEGIES FOR CONVERTING CELLULOSIC BIOMASS INTO ETHANOL

Organism	Fermentable Sugars	Synthetic-Biology Approach
Ethanol-producing	C-6 only	Introduce metabolic pathway to allow C-5 carbon conversion to ethanol
Nonethanol producing	Both C-5 and C-6	Introduce ethanol-producing pathway

Source: BCC Research

One approach is to engineer a metabolic pathway that allows ethanol-producing yeast to ferment 5-carbon sugars into ethanol. Iogen Corp. is using this approach. A second strategy is to engineer the ability to produce ethanol into an organism that naturally uses a wide range of sugars. Verenium is using this approach, where genes for the ethanol pathway of *Zymomanas mobilis* (a bacterium used in the Mexican alcoholic beverage pulque) have been added to *E. coli*.

Two factors can drive the faster adoption of cellulosic biomass as a feedstock for the biofuel industry: better and less-expensive enzymes and lower capital costs.

Capital costs can be reduced by retrofitting existing biorefineries, and several companies are taking this approach, including Poet and Cosan.

ALGAE FEEDSTOCKS

Algae are relatively abundant and of moderate cost. It is also a nonfood feedstock. Algae are rich in oils, with nearly 50% of their weight being usable oil. Because of this, algae feedstocks are an attractive target for synthetic-biology companies. Algae have significant strategic advantages as a feedstock in terms of the biodiesel yield per acre of crop, as shown in the table below.

TABLE 36

BIODIESEL YIELD OF SELECTED CROPS
(GALLONS/ACRE/YEAR)

Crop	Biodiesel Yield
Micro algae	15,000
Palm oil	635
Rapeseed	125
Sunflower	100
Safflower	83
Soybean	47

Source: BCC Research

As seen in the table, algae can produce 300 times the amount of oil per acre than soybeans and 24 times greater than palm oil. Micro algae produce, on average, 15,000 gallons per acre per year, while the next best energy crop, palm oil, produces 635 gallons per acre per year.

Challenges for algal-based biofuel companies include optimizing the growth conditions so overcrowding does not occur, removing waste oxygen and providing CO_2 (usually done by locating close to a power station).

Other factors that must be considered include which particular algal species to use – salt or fresh water species – and whether to grow the algae in closed or open ponds.

Algae have other potential advantages as a biofuel feedstock, including the following:

- The short life cycle (six hours to eight hours) of algae increases productivity.
- Algae allow for reduction in arable land use required for biofuel production. Algae grow distant to farmland or forests and minimize impact on the ecology or food-chain systems.
- Algae can grow near power plants or in sewage, and therefore pollution treatment and biofuel production can be combined.
- Since algae consume nondrinkable (e.g., salt or brackish) water, fresh drinkable water can be conserved for populations.
- Algae have the potential for converting to kerosene; a component of jet fuel. There are few choices for jet fuel: ethanol does not have high enough energy density, and diesel is dense enough but solidifies at the low temperatures of high altitude flight. Jet fuel is just 8% of petroleum use and has few renewable sources.
- Algae consume CO_2 (a global warming gas) and produce oxygen.

Microorganism strains are critical to the development of algae technology platforms. Desirable features include high lipid (oil) content, flexible temperature and pH range, evaporation, tolerance to salinity and resistance to invasion by outside organisms. Synthetic-biology tools are particularly useful for genetically engineering these features into microorganism strains.

CARBON DIOXIDE FEEDSTOCKS

CO_2 feedstocks do not require photosynthesis as do other biomass feedstocks. CO_2 is very abundant and a low-cost feedstock. It can be obtained from CO_2 emitters, which give them a carbon reduction credit.

BIOFUEL END PRODUCTS

Besides feedstock, the biofuel type and composition is important to the biorefinery. Choosing what product(s) to produce is an important strategic decision for a company. The fuel type produced affects all parts of the production value chain, from feedstock to microorganism to transportation and distribution of the product.

The table below compares one parameter, energy content, of various fuel types. The table shows key differences in fuel efficiency, which may also factor into a refinery’s decision-making process.

TABLE 37

EFFICIENCY OF VARIOUS FUELS
(%)

Fuel Type	Index Value
Oil-based diesel	100
BTL biodiesel	94
Biodiesel	90
Gasoline	87
Biobutanol	79
LPG	60
Ethanol	56
Methanol	46
CNG	25

BTL, biomass to liquid; CNG, compressed natural gas; LPG, liquefied petroleum gas.

Source: BCC Research; U.S. Department of Energy (IEA)

The data in the table are taken from the U.S. Department of Energy, which shows the fuel efficiency indexed to oil-based diesel. The data show that biodiesel does not differ much from conventional diesel, but that ethanol's energy content is much lower than that of gasoline. Biodiesel has an energy content of approximately 90% of conventional diesel, which means that the fuel efficiency of cars running on biodiesel is 90% of a gasoline-powered car. On the other hand, ethanol's energy content is only about two-thirds of gasoline, which means that the fuel efficiency of cars running on ethanol is only 70% of a gasoline-powered car.

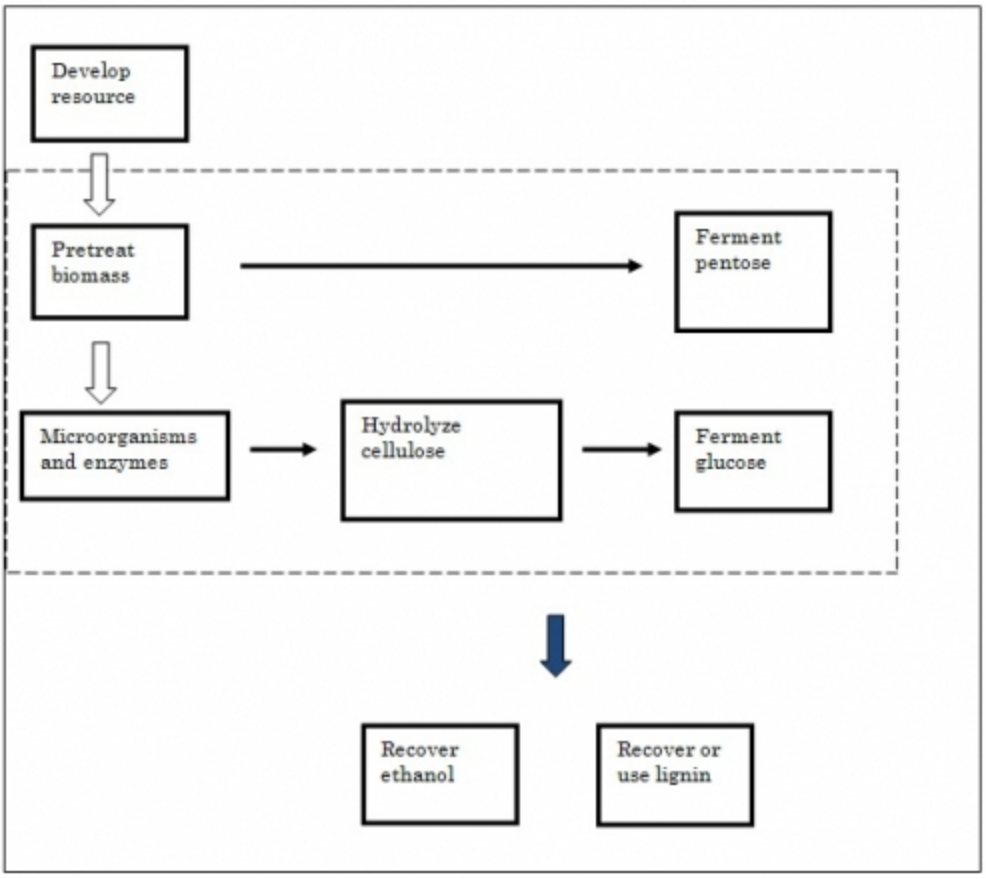
Ethanol and biodiesel are the two major biofuels in production today. Both fuels are key targets of the synthetic-biology industry. In particular, ethanol produced from cellulosic feedstocks – cellulosic ethanol – is an important strategic fuel for synthetic-biology companies.

Cellulosic Ethanol

The basic process for producing cellulosic ethanol is shown in the figure below.

FIGURE 8

CELLULOSIC ETHANOL PRODUCTION SCHEMATIC



Source: BCC Research

The technology and specifics for each step of the ethanol conversion process may differ considerably, resulting in different yields and cost structures.

In the first step, the pretreatment of biomass raw materials renders the feedstock more susceptible to hydrolysis. Pretreatment technologies include thermal and physical.

In the hydrolysis step, enzymes are added that break the plant cell walls into simple sugar molecules. In the final step, the sugars are converted to ethanol in a series of fermentation and distillation processes.

An important byproduct of the overall process is lignin. Lignin is an important component of all lignocellulosic biomass (approximately 20% by dry weight) and forms a residue in the production process. Plants with high lignin content are more desirable because they contain more energy content. The ability to convert lignin to industrial chemical products or high-value fuel additives can add to a refinery’s profit margins. Some refineries use lignin as a power source for their plant.

Costs for the ethanol production process are driven mainly by production of byproducts and the total number of processing steps required from feedstock to final products. Byproducts can represent up to 50% of the total product revenues for a cellulosic ethanol plant.

One of the goals of synthetic biology is to reduce the number of steps contained within the box in the figure above. Synthetic-biology tools allow for massive re-engineering of microorganisms to make them capable of converting the untreated biomass into final ethanol products. The complexity is transferred from the process itself to the genetic makeup of the microorganism, which performs the complex conversion steps within its own cells. Synthetic biology thus represents a potentially transformative technology for biofuel conversion.

Outstanding issues with the development of cellulosic ethanol include acceleration of the hydrolysis reaction that breaks down the cellulose fibers, and finding a commercial outlet for the lignin by-products. Strategies to lower the production costs include more selective and efficient enzymes, reducing the number of fermentation steps and better pretreatment processes that allow more efficient hydrolysis of the feedstock.

Biodiesel

Biodiesel, a second important biofuel, is produced via the Fischer–Tropsch process using natural gas (gas to liquid [GTL]), coal (coal to liquid) or biomass (biomass to liquid [BTL]). GTL is the most mature process; however, it is costly and not a domestic source of energy for most countries, which limits its use.

BTL is the most promising of these three technologies. BTL uses biomass such as wood waste, strain, grain waste, garbage, or sludge and sewage, which form carbon monoxide (CO) and hydrogen (H) under steam and catalyst. CO and H react to form hydrocarbons and water. A key advantage of BTL is its use of low-cost, readily available domestic resources.

An important consideration when evaluating biodiesel feedstocks is the feedstock iodine value. Iodine value indicates the number of double bonds in oil, because, when added to oil, iodine breaks all of its double bonds. Thus, if oil has a high number of double bonds, its iodine value will be high and the temperature at which it solidifies will be low (double bonds reduce oil’s ability to solidify). A fuel’s solidification temperature can be expressed as its melting point, cloud point, cold filter plugging point or pour point; each one of these means essentially the same thing.

The table below shows the iodine number of several different types of oils.

TABLE 38

IODINE NUMBER OF VARIOUS OILS

Oil	Melting Range	Methyl Ester	Iodine Number	Cetane Number
Rapeseed	–5	–12	110 to115	58
Sunflower	–18	–12	126 to135	52
Olive	–12	–6	77 to 94	60
Soybean	–12	–10	126 to140	53
Cotton seed	0	–5	100 to115	56

Coconut	20 to 24	–9	8 to 10	70
Palm	30 to 38	14	44 to 58	65
Tallow	35 to 40	16	50 to 60	75
Lard	32 to 36	14	60 to 70	65

Source: BCC Research; Union zur Forderung von Oel- und Proteinpflazen (UFOP)

Countries specify quality standards for iodine value, and the oil must meet these standards. In the case of the E.U., the largest user of biodiesel fuel, rapeseed oil is the only feedstock that meets its iodine value standard.

Other Biofuels

Biofuels other than ethanol or diesel are being developed by the synthetic-biology industry, including isobutanol, biocrude and jet fuel. The driving force for these projects is the need for a better biofuel.

Despite its present high market share, ethanol, for example, has several disadvantages as a fuel. It is highly corrosive and must be diluted with gasoline by 90% in conventional engines. Because ethanol mixes with water, it must be distilled, which is an energy-intensive process. Finally, ethanol is less energy dense than gasoline, which reduces the mileage per gallon.

Alternative fuels are desirable because they have higher energy content, are less corrosive or are easier to recover. Several synthetic-biology companies are pursuing these alternative fuels in their programs.

Role of Genetic Engineering and Synthetic Biology in Biofuels

As we have discussed, there is a technology gap in biomass-conversion technologies that synthetic-biology companies can exploit: the need to optimize the yield and quality of biomass. This can be accomplished through synthetic-biology tools by either making genetic modifications to the biomass source itself (e.g., the genomics approach that Synthetic Genomics is taking toward palm oil sources) or by creating massively genetically engineered microorganisms that can improve the refining process. In addition, enzymes that break down cellulose can be genetically improved and reduced in cost.

The table below describes the contributions of genetic engineering and synthetic biology to biofuels development. Both fields have made important contributions. Genetic engineering has made significant contributions to feedstock trait modification, yield improvement and the manufacturing process (e.g., through improvements in cellulose enzymes).

Synthetic biology is a key technology in designing novel organisms that can break down cellulose or convert breakdown products into fuels. This capability significantly expands feedstock choices beyond food crops to include cellulosic biomass and CO_2.

TABLE 39

CONTRIBUTION OF SYNTHETIC BIOLOGY TO BIOFUELS

Contribution Area	Genetic Engineering	Synthetic Biology
Trait modification	Disease resistance; stress tolerance	
Feedstock conversion	Cellulases (key enzymes that break down cellulose); yeast diet	Engineered organisms that break down cellulose or convert breakdown chemicals to fuels
Feedstock choices	Trait modification and yield improvement for existing feedstocks	Allows significant expansion of feedstock choices to include cellulosic and CO_2

CO_2, carbon dioxide.

Source: BCC Research

Synthetic biology has made two key contributions in the area of cellulosic feedstocks: reduction of the high costs of cellulose enzymes and creation of novel microorganisms able to ferment the cellulose breakdown products. Engineering microbe strains that can break down both hexoses (e.g., glucose) and pentoses (from the breakdown of hemicelluloses) have been important technical contributions of synthetic biology.

SYNTHETIC-BIOLOGY INITIATIVES

Synthetic biology is driven by innovations in technologies and tools, many of which are developed as part of specific projects. Examples of recent synthetic-biology initiatives are given in the table below.

TABLE 40

SYNTHETIC-BIOLOGY INITIATIVES

Program	Description
Boston University Microbiome Initiative	Synthetic-biology tools used in study of the microbiome
Human Genome Project-Write	Develop new tools for synthesizing large DNA constructs
National Microbiome Initiative	Integrate the study of microbiomes across disciplines, bringing synthetic-biology tools to bear
Novartis Collaboration	Use synthetic-biology tools to mine microbiomes to discovery drugs
Sc2.0	Develop the tools to synthesize a complete yeast genome

Source: BCC Research

The Boston University Microbiome Initiative focuses on using synthetic-biology approaches to studying microbial systems.

The Human Genome Project-Write (HGP-Write) is a proposed large-scale initiative to follow on from the original Human Genome Project (HGP-Read).[4] The proposed goal of this initiative is to develop tools and technologies for lowering the cost of designing, synthesizing and testing large genomes (0.1 billion to 100 billion bp in length) in cell lines by a factor of 1,000 over current methods. $100 million is being sought to get the project started.

The potential significance of this initiative, if it comes to fruition, is that it not only reduces the cost of designing and synthesizing large genomes, but will result in spin-off technologies that will aid the synthetic-biology industry. The initial technologies that will be used will include standardized gene parts, whole-genome synthesis platforms and gene-editing platforms.

Promising applications that are envisioned for HGP-Write include ultrasafe (e.g., resistant to viruses and cancer) mammalian cell lines for recombinant protein production and engineered genetic circuits for microbial production.

The National Microbiome Initiative, sponsored by the White House Office of Science and Technology, seeks to use synthetic-biology tools to study various types of microbiomes. Technology approaches in this industry include fecal microbiota transplants (ingesting the healthy stool of someone else), defined mixtures, small molecules and engineered bacteria. Synthetic-biology approaches are used for engineered bacteria.

In 2016, Novartis formed a microbiome collaboration with four institutions – the University of California, San Francisco; The Broad Institute; Massachusetts Institute of Technology; and Harvard University – to discover pharmaceuticals by mining microbiome data. The collaborators will use synthetic biology, bioinformatics, natural-products chemistry and high-throughput discovery assay tools for this effort.

The objective is to predict the many thousands of chemicals that microbiomes can produce; study these molecules to determine how they affect physiology; and use this information to develop a new class of pharmaceuticals.

The goal of the Sc2.0 Project is to synthesize an extensively edited yeast genome. The Sc2.0 Project is sponsored by a consortium of universities and companies with expertise in these fields.

[4] Boeke et al, Genome engineering. The genome project-write, *Science*. 2016, 353 (6295), 126–7.

Chapter 5

SYNTHETIC-BIOLOGY APPLICATIONS

SYNTHETIC BIOLOGY: GLOBAL MARKETS

BIO066D
January 2017

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ISBN: 1-62296-433-0

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CHAPTER 5
SYNTHETIC-BIOLOGY APPLICATIONS

ENABLING TECHNOLOGIES APPLICATIONS

The table below shows the enabling technologies of synthetic biology together with the corresponding products that are enabled by each technology.

TABLE 41

SYNTHETIC-BIOLOGY PRODUCTS IMPACTED BY ENABLING TECHNOLOGIES

Enabling Technology	Synthetic-Biology Products Impacted
DNA sequencing	Biologic parts; pathway engineering; cellular factories
DNA synthesis	Biologic parts; synthetic organisms; cells and chromosomes
Genome editing	Synthetic-biology research tools, and downstream products in agriculture, animals and therapeutics
Cell culture media	Cellular factories
Microfluidics	DNA synthesis and sequencing
Bioinformatics	Gene optimization software (optimizing codon usage, mRNA secondary structures, splicing motives, reverse ORFs, ribosome binding sites); comparative genomics software (i.e., BLAST)

mRNA, messenger RNA; ORF, open reading frame.

Source: BCC Research

DNA sequencing is important as a quality control technology in biologic parts synthesis. It also is critical to pathway engineering and cellular factories, by identifying which genes are responsible for producing a given biologic product. Access to large databases containing the DNA sequences of a wide range of organisms is critical to finding these genes. Such databases have become possible only very recently with the emergence of next-generation, low-cost DNA-sequencing methods.

Low-cost, efficient DNA synthesis is critical for manufacturing the range of biologic parts used in synthetic biology. DNA synthesis is also required for creating synthetic organisms, cells and chromosomes.

Genome-editing tools allow for efficient insertion, deletion or other modifications to be made to an organism’s genome. Recent tools, including cluttered regularly interspaced short palindromic repeats (CRISPR)/Cas9 technologies, have led to an increase in the level of activity in this field. Companies are focused on the following four main applications: life science research; agriculture; animals; and therapeutics.

Cell culture media (e.g., basal media, animal sera, balanced salt solutions, serum free media, dry powdered media, and growth and attachment factors) are critical for maintaining the viability of cellular biofactors used in synthetic biology.

Microfluidics (DNA microarrays and lab-on-a-chip) are important to DNA sequencing and synthesis.

Bioinformatics technologies are important in a number of areas of synthetic biology. In gene synthesis, software is used to optimize the design gene sequence to achieve better performance (e.g., protein-expression levels in specific host cells). Comparative genomic software is critical to gene-synthesis companies that need to monitor customer orders against select agents (those pathogens flagged as potential bioweapons).

BIOLOGIC COMPONENTS AND INTEGRATED SYSTEMS APPLICATIONS

Biologic components are used to assembly more complex systems, such as producer cells. For example, synthetic genes for specific enzymes can be inserted into producer cell genomes such as *E. coli*. The table below provides a list of important biologic components and integrated systems, together with their key applications. These components are used in many applications essential to many areas of synthetic biology.

TABLE 42

BIOLOGIC COMPONENTS AND INTEGRATED SYSTEMS NEAR-TERM APPLICATIONS

Component/System	Applications
Synthetic genes	Protein expression in heterologous systems; parts for vectors, genomes; directed-evolution assays
DNA constructs (e.g., BioBrick and iGEM parts)	Gene regulation; gene-expression promoters; parts for metabolic pathway engineering
Chassis organisms and cell factories	Development of new microbial expression systems; improvement in existing expression systems
Synthetic cells and tissues	Research tool to understand interactions of cells within the body

iGEM, Intercollegiate Genetically Engineered Machine.

Source: BCC Research

Synthetic genes are an essential component of synthetic-biology processes today, with DNA constructs also increasing in significance as more complex systems are created. Chassis organisms and cell factories are platforms for expressing enabled products in chemicals, pharmaceuticals and energy. Synthetic cells and tissues are limited today to research applications, but have wider long-term commercial potential.

SYNTHETIC GENES

Synthetic genes are mostly for completely new genes that have not been synthesized before. This is because genes that have already been synthesized are easier to replicate using well-known vectors rather than being synthesized again.

After the synthesized gene is sent to the customer, its sequence and quality is readily verified using next-generation sequencing methods. In addition, the production of large quantities of the newly synthesized gene is done using vectors such as bacteria, ovaries, plants or animals.

The synthetic gene can be used as a key tool in synthetic biology to develop biologic production organisms capable of making products. For example, novel synthetic genes can be used to construct nonpathogenic microbial strains capable of producing high-quality industrial enzymes.

The table below describes several near-term applications of synthetic genes.

TABLE 43

SYNTHETIC GENES NEAR-TERM APPLICATIONS

Application	Primary End Users
Protein-expression optimization in heterologous systems	Academia, pharmaceuticals, agricultural biotechnology
Building blocks for vectors and genomes	Academia, biotechnology
Construction of gene disruption cassettes	Academia, biotechnology
Directed molecular evolution	Academia, industrial biotechnology
Site-directed mutagenesis	Academia, biotechnology
DNA vaccine optimization	Biotechnology, pharmaceuticals
cDNA synthesis	Academia, biotechnology, pharmaceuticals
Creation of gene variants	Biotechnology, pharmaceuticals
Alternative splice variants	Biotechnology, pharmaceuticals

cDNA, complementary DNA.

Source: BCC Research

Gene synthesis is rapidly replacing cloning as a molecular-biology tool, particularly for the following applications: (1) rare genes with low copy number transcripts; (2) large genes; or (3) genes from bacteria living in extreme environments or from virulent pathogens that are difficult to obtain. One of the problems with cloning is adapting a mammalian gene to its bacterial or yeast host. Expression of the gene in the new host may be low because the genetic code differences among species. Synthetic genes circumvent this issue by revising the genetic code of the mammalian gene so that the host organism can easily read and at the same time produce the identical protein.

In a site-directed mutagenesis experiment, structural biologists may want to remove all of the cysteines from a receptor or channel for a cysteine cross-link experiment. Using conventional techniques, the cysteines are removed one at a time. Using synthetic genes, all of the cysteines can be removed at the same time.

A significant application is protein expression in nonnative (heterologous) host organisms. Synthetic genes are particularly useful for this application because they can be modified to more efficiently express messenger RNA (mRNA) in a foreign host system, and the

expressed protein can be more readily extracted and purified. Heterologous systems can be better adapted for large-scale extraction and purification, and quality control and thus are less costly and produce higher-quality protein products.

The sequence of synthetic genes can be easily optimized for important factors such as codon bias, which affects gene expression. The pattern of codon usage varies among organisms, and for a given host organism, the codon usage pattern should be optimized to achieve high expression levels. Codon optimization is a key informatics tool that gene-synthesis companies use to differentiate themselves. Codon optimization is often combined with other sequence modification (e.g., secretory signal sequences, guanine–cytosine content, mRNA secondary structures) to improve yields.

Besides protein expression in research and development tools, synthetic genes have been used in the pharmaceutical industry to enhance the efficacy of DNA vaccines, cardiovascular gene therapy and increasing expression of active HIV-1 integrase in human cells. In agricultural biotechnology, synthetic genes can be used for crop improvements (yield, quality and resistance to diseases).

Synthetic genes are a critical technology for synthesis of long, accurate DNA sequences, such as plasmids or whole genomes.

Synthetic genes can be used to assemble more complex DNA constructs, and they provide a simple way to study gene disruption. Gene knock-out lines are useful molecular-biology tools to study physiological processes, and a number of molecular-biology methods are used for targeted gene deletion. Conventional methods include isolation of the gene and digestion with restriction enzymes, Cre-loxP systems and polymerase chain reaction (PCR)-based strategies. These methods suffer from limitations including lack of restriction sites and multiple PCR steps.

The rational design and modification of genes using synthetic tools can provide an attractive path for directed molecular evolution. Molecular evolution is particularly useful for optimizing industrial enzymes, for which selections do not already exist. In altering the structure of a protein in a directed-evolution experiment, it is not always known if the active site or other sites should be targets. Also, in some cases, the active site or key residues are not known for the protein.

DNA-synthesis tools are also useful for creating libraries of protein variants, since every amino acid in the protein can be easily changed. These protein-variant libraries are very useful for directed evolution to design better enzymes or other proteins.

DNA vaccines have many advantages over traditional vaccines, but they are limited in their application by such factors as delivery, safety and efficacy. Gene synthesis can be used to increase the safety profile and efficacy of a DNA vaccine by optimizing the vector, transgene and supporting additives. In vivo properties of the vaccine, such as immune response, RNA and protein stability and recombination risk, can also be optimized. Applications include DNA vaccines for cancer and infectious diseases; transgenes and vectors for therapy; DNA vaccine libraries for pathogen genes; and optimized efficacy, safety and immunogenicity for DNA and RNA vaccines.

Gene synthesis is an efficient method to produce complementary DNA (cDNA) or library constructs. Because there is no requirement to splice short fragments, a full-length cDNA can be produced in a short time period. cDNA for rare species can be synthesized using only the nucleotide sequence, and repeat sequences and secondary structure can be optimized for increased protein-expression yield.

In human medicine, genetic deletions and insertions can result in severely altered or even nonfunctional proteins, resulting in disorders. Point mutations and epigenetic changes may also cause disorders. Because of this, gene variants are becoming more important for studying the relationship between genotype and phenotype. Many gene variants are difficult to create by PCR amplification or other methods. Gene-synthesis technology provides an efficient way to create variant genes or cDNAs, with DNA deletions, insertions, rearrangements, point mutations or epigenetic changes at specific target sites. This synthetic-biology tool enhances a researcher’s ability for creating epigenetic modifications to regulate gene expression, developing gene therapies or making synthetic-gene variants.

Alternative splicing permits a single pre-mRNA to be transcribed into different isoforms, meaning that the resulting proteins can have different functions. Alternative splicing is a key aspect of the functional complexity of the genome, and its study is important to biomarker discovery, drug development and gene identification. Current methods of synthesizing splice variants are difficult because alternative splicing occurs frequently and is hard to control and genes produce many thousands of transcripts, requiring a new model for each alternative splice. Synthesis of alternative splicing genes can be an efficient way to perform experiments in this important research field.

BIOBRICK PARTS

BioBrick parts are currently used primarily in life science research applications. They are particularly useful to synthetic biology because each piece of DNA is tagged on each side with DNA connectors, allowing the pieces to be easily interchanged.

BioBricks are enabling to synthetic biology because they are well-characterized, standardized, modular DNA constructs that allow plug-and-play capability and provide predictable behavior.

A key feature of BioBrick parts is that they have standard ends, so that they can be combined in any order to create a new BioBrick, and so on. This allows large and complex DNA constructs to be built from a library of standard components.

Gene switches are a key application, since they can be used to control gene expression in many applications. For example, enzymes that have been optimized for producing certain functions, such as breaking down cellulose, can be controlled using protein switches. Gene switches are useful tools for research in many areas of functional genomics and design of protein production systems.

BioBrick parts can also be used as gene-control circuitry in transgenic animals for controlling when a gene is expressed.

Synthetic biologic parts can be used to encode for reporter molecules that fluoresce, for example, when a gene is transcribed.

Synthetic promoters and reports can be used in experiments that model genetic circuitry in biologic systems.

Synthetic reporter genes can be used for on-line monitoring of fermentation processes for monoclonal antibodies (mAbs) and vaccines. The genes are inserted into a cell's genome, and they initiate production of a reporter compound when there is a change in the cell's health or growth conditions in the fermenter. The reporter compound can be detected by standard instruments such as gas chromatography–mass spectrometry, and appropriate changes can be made to optimize the fermenter.

BioBrick parts are a growing field, and several laboratories and companies are developing this technology, including Professor Howard Salis (Penn State University, salis.psu.edu/) and Ginkgo Bioworks. Ginkgo assembles synthesized pieces of DNA into functional parts. There were more than 20,000 standard BioBrick parts available from the Registry of Standard Biological Parts (maintained by the Massachusetts Institute of Technology, www.partsregistry.org).

Modular protein domains correspond to BioBricks, but are not as far developed. One approach is novel BioBricks in which the DNA fragment encodes for protein domains. The furthest advanced system today is the zinc finger protein (ZFP) domain.

INTEGRATED SYSTEMS

Integrated systems are artificial biologic systems that perform a specific function, and they include artificial chromosomes, artificial cells, chassis organisms (rationally engineered organisms having a minimal genome as the key component) and alternative minimal systems.

Chassis organisms are stable, robust bacterial hosts with known responses. A chassis organism is adapted to specific tasks and can be used for design projects. In synthetic biology today, the approach is to take an existing organism and reduce its genome by stripping it of all nonessential parts. Then, the remaining information is restructured for achieving the purpose of the chassis.

The alternative bottom-up approach involves the design and construction of a completely synthetic cell, which can be used as a chassis organism. In March 2016, the J. Craig Venter Institute and Synthetic Genomics Inc. announced that they had designed and constructed the first minimal synthetic bacterial cell, JCVI-Syn3.0. This cell has 521,560 base pairs and 473 genes. Approximately one-third of these genes have unknown function, but are highly conserved in many species.

JCVI-Syn3.0 is a viable, self-replicating minimal synthetic cell.

The research effort resulted in new synthetic-biology tools and semiautomated processes for whole-genome synthesis. These tools included tools for combinatorial gene libraries,

genomics software, Gibson Assembly and instruments for producing accurate synthetic DNA fragments.

Escherichia coli is commonly used as a standard chassis organism, and the table below shows the advantages and limitations for its use. The main advantage is that *E. coli* is extremely well characterized, having been used for many years in life sciences. However, limitations include: a potentially toxic outer membrane; the inability to secrete proteins effectively; difficulty for long-term storage; and the possibility of generating pathogenic strains.

TABLE 44

E. COLI AS A CHASSIS ORGANISM

Advantages	Limitations
High degree of characterization	Gram negative bacterium, with outer membrane of toxic lipopolysaccharides
Many unique strains or vectors available	Cannot secrete many proteins effectively because it lacks the main terminal branch of the General Secretory Pathway
	Long-term storage requires freeze-drying or cryogenic freezing
	Pathogenic constructs may be generated

Source: BCC Research

Chassis organisms besides *E. coli* include *Mycoplasma genitalium*, *Mesoplasma florum*, *Bacillus subtilis* and *lactobacillus* spp. The last two are nonpathogenic, gram positive and good protein secretors.

The genomic systems of these bacteria are reduced to create the chassis organism. The genome of *E. coli* has been reduced by more than 15% by eliminating virulence genes or recombinogenic sequences (i.e., transposons and insertion sequence elements). The genome of *B. subtilis* has been reduced by more than 8%.

Chassis organisms are in vivo systems with reduced, adapted genomes. A different approach is alternative minimal systems, which are in vitro systems that use only parts of a cell. Examples of minimal systems include the enzyme scaffold for doing multi-enzyme synthesis and the protein translation scaffold for doing cell-free protein synthesis.

The advantage of alternative minimal systems is they can be controlled to a higher level than in vivo systems. However, these systems are not as robust because they do not access the cell’s machinery to carry out protein synthesis.

The combination of three synthetic-biology tools enables integrated systems: synthetic codon-optimized genes; artificial promoters; and microbial strains with an industrially minimized metabolism (i.e., with minimal genomes) for production that is more efficient.

Minimal genomes (in vitro) and chassis organisms (in vivo) form the basis for cellular factories that can produce valuable products.

In 2011, DARPA (Defense Advanced Research Projects Agency) announced a “Living Factories” initiative that will seek to transform the manufacturing landscape in the U.S. Subsequently, in 2013, the Russian Advanced Research Foundation (modeled after DARPA in the U.S.) listed Living Factories and synthetic biology as one of the 10 most promising high-risk research programs.

Synthetic-biology foundries use high-throughput protocols to perform genetic design, construct and analyze complex genetic programs. Foundries provide end-to-end design, construction and phenotypic analysis of small to large gene constructs or genetic circuits or pathways.

Foundries engineer microorganisms for production tasks and optimize the organism’s efficiency and output using synthetic-biology tools. Services that foundries provide include design and synthesis (e.g., construct design, DNA synthesis, genome editing, expression plasmids, artificial chromosomes) and expression and screening (e.g., scalable fermentation, expression optimization, clone screening).

ENABLED PRODUCTS APPLICATIONS

Downstream products enabled by synthetic biology covered in this section include pharmaceuticals, agriculture, industrial biotechnology and DNA storage.

Cellular factories designed using synthetic-biology tools are the key platform for synthetic-biology-enabled products. Cell factories rely on microorganisms whose genomes have been extensively re-engineered, on a scale much greater than conventional genetic engineering. Such microorganisms have experienced numerous changes to their genetic material to achieve a specific metabolic goal.

An example is DuPont’s development of an *E. coli* bacterium that produces 1,3-propanediol (a key ingredient in textiles) from cornstarch. DuPont used synthetic DNA to alter the bacterium’s genome for more efficient metabolism and efficiency.

PHARMACEUTICALS

Synthetic-biology tools are used by the pharmaceutical industry to discover new drugs, develop novel drug types or produce drugs in a more efficient way. The following applications for synthetic biology are reviewed in this section: drug discovery and development; genome editing; immuno-oncology; and other pharma.

Drug Discovery and Development

Key applications in the field of drug discovery and development are shown in the table below.

TABLE 45

DRUG-DISCOVERY AND DEVELOPMENT APPLICATIONS FOR SYNTHETIC-BIOLOGY PRODUCTS

Application	Synthetic-Biology Products
Protein-based drug discovery	Synthetic genes and gene libraries
DNA vaccine development	Synthetic genes and gene libraries
Affinity development	High variant, high fidelity gene libraries combined with secretion- and capture-display methods
Drug discovery using genetic switches	Synthetic-gene regulator switches

Source: BCC Research

Both protein-based drug discovery and DNA vaccine development require the availability of extensive libraries of mutated natural proteins. Expression of mutated proteins at a high level in a given biologic expression system is a key step in obtaining these libraries. Synthetic genes that had been designed and optimized needed protein product help to overcome this hurdle. The traditional method, PCR cloning, involves costly and time-consuming steps including PCR, DNA sequencing and sequence correction steps.

Leaders in vaccine development or production using synthetic-biology platforms include TeselaGen (software for vaccine libraries), Sutro/Sanofi Pasteur (cell-free synthesis), SutroVax (cell-free synthesis), Prokarium (engineered bacteria for in vivo vaccine release), Phylogica/Pfizer (peptide vaccines) and Synthetic Genomics/ Novartis (synthetic virus seed strains).

Maximizing protein yields in heterologous expression systems is important for providing enough material for drug design and functional work. Synthetic-biology tools can be used to optimize the gene sequences in these expression systems. The tools work by creating variant libraries of genes in which the amino acid sequences are held constant and only silent mutations are tested. These libraries may include antibody fragments. When these gene libraries are combined with suitable display methods, in vitro selection of antibodies with desired properties can be achieved. Several companies are using these technologies for antibody development, including ATUM and MorphoSys.

As seen in the above examples, pharmaceutical companies need multiple copies of genes with small sequence variations for massively parallel experiments. These experiments help researchers to understand pharmacogenomic questions, such as, why do some patients respond to drugs while others do not? Understanding this issue is critical to increasing the success rate of drug discovery and development.

Synthetic genes and gene libraries are thus important enabling technologies for increasing the success rate of drug development in the pharmaceutical industry.

Synthetic genes have reached the price point where most researchers will order a synthetic gene rather than make the equivalent molecule themselves. The use of synthetic

genes has been dramatically assisted by the availability of complete genome sequences of humans and other species in databases.

Genome-Edited Pharmaceuticals

Genome-editing platforms that are near term (i.e., feasible clinical applications during the next five years) include those detailed in the table below.

TABLE 46

GENOME-EDITING NEAR-TERM CLINICAL APPLICATIONS

Indication	Class	Company	Platform
Beta-thalassemia major	Hematological	Sangamo Therapeutics	ZFN
Severe sickle cell disease	Hematological	Sangamo Therapeutics	ZFN
SCID	Hematological	Sangmo Therapeutics	ZFN
Rare blood diseases	Hematological	Abeona Therapeutics	CRISPR/Cas9
HIV	Hematological	Sangamo Therapeutics	ZFN
ALL	Hematological	Cellectis	TALEN
CLL	Hematological	Cellectis	TALEN
Hemophilia A	Liver	Sangamo Therapeutics	ZFN
Hemophilia B	Liver	Sangamo Therapeutics	ZFN
MPS 1 – Hurler syndrome	Liver	Sangamo Therapeutics	ZFN
MPS II – Hunter syndrome	Liver	Sangamo Therapeutics	ZFN
Huntington’s disease	Brain	Sangamo Therapeutics	ZFN
LCA	Eye	Editas	CRISPR/Cas9

ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; CRISPR, cluttered regularly interspaced short palindromic repeats; HIV, human immunodeficiency virus; LCA, Leber congenital amaurosis; MPS, mucopolysaccharidosis; SCID, severe combined immunodeficiency; TALEN, transcription activator-like effector nuclease; ZFN, zinc finger nuclease.

Source: BCC Research

There are additional potential clinical markets not given in the table, which are in discovery stage and may be able to be commercialized in the more distant future. Companies with discovery programs for therapies using genome editing and other synthetic-biology approaches include Editas, Intella, Ziopharm and Abeona Therapeutics.

Specific indications that are in the discovery/research stage include chimeric antigen receptor (CAR)-T, nonmalignant hematology, DMD and cystic fibrosis (Editas discovery programs); rare genetic diseases (Abeona Therapeutics); and immuno-oncology (Inovio).

Immuno-Oncology

The field of immuno-oncology represents a strong market opportunity for synthetic-biology technologies. Immuno-oncology involves activating a patient's immune system so that it can then fight the cancer. Conventional cancer drugs attempt to directly kill the cancer. Immuno-oncology therapies have the potential to change the treatment paradigm for cancer, as they use the patient's natural immune system to fight the cancer. The potential benefits of the immuno-oncology approach include: immune enhancing, versus damage to the immune system with conventional therapy; more sustained response against the cancer because immuno-oncology "teaches" the immune system; and attacks the central mechanism of tumor growth, by evading or developing resistance to the immune system.

Immuno-oncology encompasses a wide range of therapies with different mechanisms of action. Therapeutic approaches include: immune checkpoint inhibitors; therapeutic vaccines; oncolytic viral therapy; and T-cell-based therapy.

The Immune checkpoint inhibitors, therapeutic vaccines and viral therapies make up the majority of the 2016 immuno-oncology market. These are the more traditional approaches to the market, and this industry is dominated by large-capital pharmaceutical companies

As of the end of February 2016, there are 84 active Phase III clinical trials for immune checkpoint inhibitors, and 27 active Phase III clinical trials for therapeutic vaccines/viral therapies.

Bristol-Myers Squibb, with its PD-1 inhibitor Opdivo (nivolumab), and Merck & Co, with its Pd-1 inhibitor Keytruda (pembrolizumab), are the leaders in this industry, with Roche, AstraZeneca and Merck KGaA/Pfizer also important players.

PD-1/L1 inhibitors are the key development approach for all companies.

Synthetic biology is a key technology for the next-generation immuno-oncology platform. T-cell-based therapies and T-cell approaches are being developed by smaller-capital biotechnology companies, and these companies are partnering with the major large-capital pharmaceutical companies.

In particular, CD19-targeting CAR-T-cell therapies are moving through clinical trials for hematological cancers. Companies with therapies in Phase I or II studies include Novartis (Tisagenlecleucel-T for pediatric acute lymphoblastic leukemia [ALL] and adult non-Hodgkin's lymphoma [NHL]); Juno Therapeutics (JACR015 for adult ALL and NHL, JCAR014 for B-cell malignancies and JCAR0-17 for adult/pediatric NHL); and Kite Pharma (KTE-C10 for adult NHL and pediatric/adult ALL).

The first CAR-T-cell therapy may launch as early as 2017.

Key issues for CAR-T-cell therapies include off-target side effects, manufacturing and expansion of the technique to solid tumors.

Off-target effects include cytokine release syndrome (CRS), in which T cells are activated before they are destroyed. The activated T cells release cytokines that cause systemic inflammatory response. This results in unwanted side effects in patients including high

fever, and feeling of unwellness. Technical approaches to mitigating CRS include developing CAR-T cells with “suicide switches” and/or “armored” CAR-T cells.

The complexity and cost of manufacturing CAR-T therapies is also an issue that is being addressed. For example, Pfizer/Cellectis are using gene editing of third-party donor T cells that could be used off the shelf, which would obviate the need for patient-specific (autologous) T cells.

CAR-T therapies are presently limited to CD19+ hematological malignancies. Solid tumors are more difficult to develop therapies for, as they provide very few unique targets for antibody recognition, and thus there is inefficient homing of T cells to solid tumor sites. Also, solid tumors have microenvironments that are immunosuppressive, which presents further challenges to T cell therapies.

Gene editing shows great promise in engineering of CAR-T cells for cancer immunotherapy. CRISPR/Cas9 technologies have enabled gene editing of CAR-T cells to remove proteins that activate the immune response. This allows for engineering allogeneic CAR-T cells that are derived from a single healthy donor and can be used to treat many thousands of patients.

Several CRISPR gene-editing companies have formed alliances with CAR-T-cell therapy companies. These alliances are shown in the table below.

TABLE 47

CAR-T CELL ALLIANCES AND SYNTHETIC-BIOLOGY PLATFORMS

Pharmaceutical Company	Synthetic-Biology Partner	Synthetic-Biology Platform
Baxalta	Precision BioSciences	MegaNuclease
Celgene	bluebird bio	TALEN
Celgene/GSK	CRISPR Therapeutics	CRISPR/Cas9
Johnson & Johnson	Transposagen Biopharmaceuticals	CRISPR/Cas9
Juno Therapeutics	Editas Medicine	CRISPR/Cas9
Kite Pharma	bluebird bio	TALEN
Novartis	Intellia Therapeutics and Caribou Biosciences	CRISPR/Cas9
Pfizer	Cellectis	CRISPR/Cas9
Ziopharm	Intrexon	Biologic switches

CRISPR, cluttered regularly interspaced short palindromic repeats; GSK, GlaxoSmithKline; TALEN, transcription activator-like effector nuclease.

Source: BCC Research

Juno and Novartis have advanced clinical trials. Juno’s trials include for adult ALL and NHL. Novartis’ clinical trial includes for diffuse large B-cell lymphoma.

Baxalta, through its alliance with Precision BioSciences, assessed the Arcus nuclease genome-editing technology.

In November 2014, Johnson & Johnson gained the rights to Piggybac footprint-free genome-editing technology developed by Transposagen.

The main focus of CAR-T development has been for CD19-related hematological cancers. Solid tumors are more difficult because of their immunosuppressive microenvironment.

The keys to companies using synthetic-biology approaches in this market area are to identify antigens beyond CD19 that can be targeted and to find approaches for treating solid tumors.

Finding additional antigens beyond CD19 is challenging; this is because CD19 is expressed only on B cells. B-cell elimination through CAR-T therapies is a ready way to treat B-cell leukemias and lymphomas. Also, loss of B cells is not a serious problem as intravenous immunoglobulin can be given to patients to restore lost B-cell antibody-generating function.

Potential antigen targets include CD22 in B-cell cancers and B-cell maturation antigen in multiple myeloma.

Other Pharmaceuticals Applications

The table below shows synthetic-biology-enabled drugs and vaccines that have either been launched, are in clinical trials, or are in late-stage development.

TABLE 48

SYNTHETIC-BIOLOGY-ENABLED PHARMACEUTICAL APPLICATIONS

Company	Compound	Indication(s)	Status
Agilis Biotherapeutics	AGIL-FA	FRDA	IND
Ambrx	ARX720 Relaxin	Heart failure	Phase I
Ambrx	ARX618 FGF21	Diabetes	Phase II
Ambrx	ARX788 aHER2 ADC	Cancer	Phase I
Biogen	NA	Hemoglobinopathies	Early discovery
Celgene	Antibodies	Undisclosed	Production of drugs
Demuris Ltd.	Antibiotics	Infectious diseases	Preclinical development
DSM	Cephalexin, cephalosporins	Infectious diseases	Launched 2006
DSM	B12, Aldolses	Cholesterol-lowering drugs	Launched
EnBiotix Inc.	EBX-001	Infections in CF patients	Preclinical development

EnBiotix Inc.	EBX-002	Antibacterial	Preclinical development
Evolva/Emergent Biosolutions	GC-072	Bacterial infections	Preclinical development
Evolva/Serodus	EV-077	Diabetes	Phase IIa
Huvepharma	Artemisinin	Malaria	Commercial
Intrexon	Various programs	Multiple applications	Preclinical development
Merck	Januvia	Diabetes	Commercial
MorphoSys	Therapeutic antibodies	Multiple applications	Phase II
Pfizer/ MorphoSys	Utomilumab	Cancer	Phase I/II
Prokarium	Vaccine	*Chlamydia trahomatis*	Preclinical development
Prokarium	Vaccine	*Chlostridium difficile*	Preclinical development
Sangamo Therapeutics	SB-728-T	HIV	Phase II
Seqirus	Flucelvax	Influenza	Commercial
Shire	NA	Monogenic diseases	Early discovery
Soligenix	SGX943	Melioidosis	Fast Track development
SutroVax	Vaccines	Infectious diseases	Production of vaccines
Synthetic Biologics	SYN-200	PKU	Discovery
Synthetic Biologics	SYN-005	Pertussis infection	Discovery
VG Life Sciences	MDT	Cancer	Phase I
Ziopharm	AD-RTS-IL-12	Melanoma and breast cancers	Phase Ib

CF, cystic fibrosis; FRDA, Friedreich’s ataxia; HIV, human immunodeficiency virus; IND, investigational new drug; NA, not available; PKU, phenylketonuria.

Source: BCC Research

Agilis Biotherapeutics is focusing its synthetic biology effort on therapeutics for rare genetic disease. The company’s lead synthetic-biology-based program is aimed at Friedreich’s ataxia (FRDA), a neurodegenerative disease. Agilis is partnered with Intrexon in this program, and has access to Intrexon’s UltraVector platform. An optimal DNA construct has been selected and nonclinical investigational new drug (IND)-enabling studies are in process.

Ambrx is developing several drugs that use nonnatural amino acids.

ARX788 aHER2 ADC (oncology) is in Phase I clinical trials. Partnered programs include ARX618 FGF21 for diabetes (Bristol-Myers Squibb, in Phase II clinical trials), ARX720 Relaxin for heart failure (Bristol-Myers Squibb, Phase I) and Imrestor for mastitis in cattle (Eli Lilly, Phase II).

Biogen is in the early stages of collaboration with Sangamo Therapeutics to discover and develop therapeutics for hemoglobinopathies, including for sickle cell disease and beta-thalassemia.

Cellgene Corp. collaborated with Sutro to use Sutro's Xpress cell-free protein synthesis platform for manufacturing of antibodies for undisclosed drug targets.

Antibiotics are particularly well suited to synthetic-biology approaches because antibiotic production is regulated by complex cellular networks and involves multistep biosynthetic pathways. In addition, there is a strong market need for new antibiotics because of the emergence of multidrug resistant pathogens.

DSM improved an existing manufacturing process for cephalexin (a semisynthetic cephalosporin) using synthetic-biology approaches. DSM developed the process using a penicillin-producing microbial strain. By introducing genes encoding acyltransferase and expandase, a one-step direct fermentation of adipoyl-y7-ADCA was accomplished. This product can be converted to cephalexin in two enzymatic steps, improving on the previous 13-step process.

DSM produces vitamin B_{12} and aldolases for cholesterol-lowering drugs using its synthetic-biology technologies.

EnBiotix is developing two engineered bacteriophage products, EBX-001 and EBX-002, for the antibacterial markets. EBX-001 is intended to be given together with tobramycin to combat *Pseudomonas aeruginosa* infections among CF patients. EBX-002 is an optimized vancomycin to be given together with low doses of silver for a range of infections.

Evolva has partnered its two pharmaceutical development projects, EV-077 and GC-072. EV-077, partnered with Serodus, is being developed for diabetic nephropathy and is in Phase IIa clinical trials. GC-072, partnered with Emergent Biosolutions, is a bacterial topoisomerase inhibitor for treating bacterial infections, and is in preclinical development.

Huvepharma purchased the synthetic-biology-based semisynthetic artemisinin plant from Sanofi in 2016. This acquisition allowed Huvepharma to control the full value chain for semisynthetic artemisinin.

Several companies, including MorphoSys and Intrexon, have wide-ranging programs for drug development using synthetic-biology tools. Intrexon emphasizes exclusive channel collaborations and relies on its partners to develop the drug. Intrexon's focus is on partnered programs in gene therapies; these programs include for wet age-related macular degeneration (partnered with Sun Pharma), collagen replacement in rare diseases (Fibrocell) and FRDA (Agilis).

MorphoSys developed unique synthetic-biology-based antibody development platforms, and uses both collaborators (e.g., major drug firms) and its own development.

MorphoSys is focused on developing therapeutic antibodies, and has 14 programs, including six in preclinical or clinical phases. Three key programs are MOR103 for rheumatoid arthritis and osteoarthritis of the hand (in Phase II and licensed to

GlaxoSmithKline), MOR202 for multiple myeloma (in Phase II) and MOR208 for chronic lymphocytic leukemia and NHL (in Phase II and licensed from Xencor).

Sitagliptin, the active ingredient of Januvia, is a first-in-class dipeptidyl peptidase-4 inhibitor for treating Type 2 diabetes. Merck & Co. and Codexis collaborated to develop a synthetic-biology-enabled route of synthesis for this drug, which uses a transaminase that allows a new biocatalytic manufacturing route. This process has been scaled-up for commercial manufacture. Januvia is a top-selling drug for Merck, with annual sales of around $4 billion.

Seqirus (formerly Novartis) worked with the J. Craig Venter Institute, the Centers for Disease Control and Synthetic Genomics Vaccines to develop flu vaccines using synthetic biology. In this collaboration, synthetic genes of flu viruses are used to develop candidate vaccine strains. The availability of synthetic genes can help to more rapidly develop a vaccine against that virus and deploy a global response to an emerging flu strain.

The key role that synthetic biology plays in this process is to create seed strains of the virus, from which influenza vaccines can be developed. The seed strain is the starter culture of the virus, and it can be used to create larger quantities of the vaccine virus.

This process effectively moves the vaccine strain production from an egg-based process to a cell-derived process, with the following advantages: (1) potential for a shorter vaccine lead time and; (2) potential for much better strain match.

Seqirus' Flucelvax Quadrivalent vaccine was approved by the U.S. Food and Drug Administration (FDA) in May 2016. This vaccine helps protect against two influenza A viruses and two B viruses. The vaccine is manufactured in Holly Springs, N.C., using a full-scale cell culture vaccine manufacturing strategy.

Pfizer has collaborations with two synthetic-biology companies for drug discovery and production. Pfizer collaborates with MorphoSys to develop and test Utomilumab, an immunotherapy that activates T cells. This compound is in Phase I/II trials.

Prokarium is using synthetic-biology tools to engineer immune-cell-targeting bacteria that express vaccines from within the human body. This oral vaccine platform is called Vaxonalla.

Prokarium's main programs are vaccines against *Chlamydia trahomatis*, a common sexually transmitted infection, and *Chlostridium difficile*, which causes potentially fatal colitis. Both of these programs are in preclinical development.

Sangamo Therapeutics's lead gene-editing (zinc finger DNA binding proteins) drug candidate is SB-728-T, for treatment of HIV/AIDS. This drug is in Phase II and Phase I/II clinical trials. In addition, Sangamo Therapeutics is involved in ZFP-based clinical studies for hemophilia B and MPS1 (lysosomal storage disorder, LSD) and preclinical programs in hemophilia A and other LSDs. In February 2016, the FDA cleared the investigational new drug for the MPS1 product.

Shire is collaborating with Sangamo Therapeutics to discover and develop drugs for treating monogenic diseases, including hemophilia and Huntington's disease. Sangamo

Therapeutics is contributing the gene-editing technology for this effort.

Soligenix is using Intrexon synthetic-biology tools to develop a therapy for treating melioidosis. SGX943 is a synthetic peptide that has a novel mechanism of action with anti-inflammatory and anti-infective activity. The drug candidate received FDA's "Fast Track" designation in May 2016.

Melioidosis is caused by *Burkholderia pseudomallei*, a bacterium that is a high-priority biodefense threat and can be spread by aerosol.

SutroVax is a joint venture of Sutro and Johnson & Johnson that is using Sutro's Xpress cell-free platform for developing new vaccines for a range of diseases.

In August 2012, Synthetic Biologics formed a partnership with Intrexon to develop and commercialize synthetic-biology-derived mAb therapies for treating infectious diseases.

This collaboration addresses the pressing problem of multidrug resistant bacteria, as mAbs may be able to destroy the microbes and neutralize their toxins. Two projects in the research phase include SYN-005 (targeting critically ill infants with pertussis) and SYN-200 (targeting patients with phenylketonuria).

VG Life Sciences uses Metabolic Disruption Technology (MDT) to develop cancer drugs. MDT compounds are used in the treatment of cancers, and there is one compound that has completed in initial Phase I clinical trial.

Ziopharm is using several synthetic-biology tools to develop a new class of cancer therapeutics based on mesenchymal lineage cells, which target specific tumor cells. The clinical stage product candidate is Ad-RTS-IL-12, which is being evaluated in combination with the oral activator veledimex for treating metastatic melanoma and unresectable recurrent or metastatic breast cancers. This drug candidate uses Intrexon's Ultra Vector and RheoSwitch Therapeutic System technologies.

INDUSTRIAL BIOTECHNOLOGY APPLICATIONS

The main applications for synthetic-biology-enabled industrial biotechnology include biofuels and chemicals (including specialty chemicals, cosmetics, and flavors and fragrances).

Biofuels

Advanced biofuels include those renewable fuels that can replace petroleum-based gasoline or diesel fuels. Synthetic-biology tools are becoming important in the production of advanced biofuels. The table below shows the main applications for advanced biofuels, together with the companies using synthetic-biology tools.

Biofuel types include cellulosic ethanol, diesel, gasoline, butanol and other (jet fuel and biocrude). Diesel was the first advanced biofuel to reach the commercial production stage. Diesel can be biodiesel or renewable diesel.

These fuels can be further categorized based on whether they are “drop-in” or specialty fuels. Drop-in fuels are those that can be processed through existing infrastructure and combustion engines. Drop-in fuels include renewable diesel and gasoline.

TABLE 49

SYNTHETIC-BIOLOGY-ENABLED BIOFUELS APPLICATIONS

Biofuel	Company
Ethanol	Agrivida, Algenol Biofuels, BP, DuPont, DSM/Poet, Glycos Biotechnologies, Iogen, Joule, Qteros, Sea6 Energy, BASF (Verenium)
Renewable Diesel	Amyris, BP, Joule, Renewable Energy Group (LS9), Sapphire Energy, TerraVia
Butanol	Butamax Advanced Biofuels (BP/DuPont, Gevo, Green Biologics/Easy Energy Systems.
Renewable Gasoline	Sapphire Energy
Other (jet fuel, biocrude)	Amyris (diesel), ExxonMobil/Synthetic Genomics, Gevo (jet fuel), Global Bioenergies/Audi (iso-octane), Sapphire Energy (jet fuel), TerraVia (jet fuel)

Source: BCC Research

The table below contrasts the growth status of specialty fuels versus drop-in fuels.

TABLE 50

GROWTH STATUS OF SPECIALTY VERSUS DROP-IN BIOFUELS, 2000-2020

	Growth	
Biofuel Type	2000–2010	2011–2020
Specialty fuel	High	Moderate
Drop-in fuel	Low	High

Source: BCC Research

Applications for drop-in fuels will grow in the future. Drop-in fuels are becoming more important to the industry because they have a low carbon intensity value, can be easily incorporated into existing fuel infrastructure, and have a high energy content compared with ethanol.

Chemicals

Synthetic biology is an open-ended technology that allows for production of industrial products on a wide scale. In the chemicals industry, this means that the technology can be used to produce a variety of products, from short-chain hydrocarbons to longer-chain hydrocarbons to aromatics.

The table below shows the main chemical applications for synthetic biology. Initial applications of the technology include bioprocessing routes to producing enzymes, polymers, cosmetics, food and agriculture, drugs, specialty aromatic chemicals, oils and acetates.

TABLE 51

SYNTHETIC-BIOLOGY-ENABLED CHEMICALS APPLICATIONS

End-Product Market	Chemical
Various industrial	Enzymes
Polymers	Acrylic acid
	Propane diol[1]
	BDO[2]
	ADA
	PHAs
	Adiponitrile
	Esters[3]
Cosmetics	Alguronic acid
Food, agriculture	Terpene
	Succinic acid[4]
	Vanillin
	Resveratrol
	Lactic acid
	Food ingredients
Drugs	Chiral intermediates
Other	Isoprene
	Specialty oil
	Aromatics
	Acetates

[1]Also used in cosmetics, antifreeze and heat-transfer fluids.
[2]Also used in solvents and fine chemicals.
[3]Also used in plastics, fragrances and adhesives.
[4]Also used in plasticizers and coatings.
ADA, adipic acid; BDO, 1,4-butanediol; PHA, polyhydroxy alkanoate.

Source: BCC Research

Synthetic biology enables more efficient and lower cost ways of making chemicals. A common approach for applying synthetic biology involves optimizing specific enzymes through directed evolution or other techniques, and integrating them into the metabolic pathway of a foreign cell producer system. Using these methods, the production efficiency can be significantly improved over conventional methods.

An example of this is succinic acid. Synthetic-biology tools allowed DSM to develop recombinant yeast capable of converting cellulose to simple sugars. Based on this

technology, DSM and Roquette Freres developed a production process for renewable succinic acid. The fermentation and recovery process is lower cost than the conventional process, thus permitting new uses for this chemical.

Similarly, modifications to metabolic pathways within *E. coli* have led to a better route to producing propanediol from glucose. Propanediol is a key intermediate for the DuPont polymer Sorona.

AGRICULTURE AND ANIMALS APPLICATIONS

The main applications for synthetic biology in agriculture and animals are shown in the table below. These include engineered plant and insect systems, genome-edited non-GMO (genetically modified organism) crops and genome-edited livestock.

TABLE 52

SYNTHETIC-BIOLOGY-ENABLED AGRICULTURE AND ANIMALS APPLICATIONS

Application	Modified Species	Example Companies
Genome-edited crops	Various food crops	Cibus, Monsanto, DuPont, Dow AgroSciences, others
Engineered plant and insect systems	Moth, mosquito, fruit fly, bollworm	Oxitec
Genome-edited livestock	Dairy cow, beef cattle, pigs	Recombinetics, Synthetic Genomics

Source: BCC Research

The companies mentioned in the table use synthetic-biology tools to engineer key properties and functions in plants, insects or animals.

For example, Oxitec is using synthetic-biology tools for controlling pest insects (e.g., moths, mosquitoes, fruit flies and bollworms). The tools, engineered into parents, can be used to render offspring incapable of surviving in the wild.

Modifying plants via genome-editing tools is a key application for agriculture.

Genome-editing tools can be used to modify plants to achieve higher yields, biotic and abiotic resistance, higher product quality (e.g., flavor, aroma, color, etc.) and better characteristics (e.g., high-cellulose cotton). The use of new genome-editing tools based on synthetic biology provides many benefits to agricultural companies. Among these are precision and specificity of gene modification, speed to market and reduced regulatory oversight.

Cibus launched sulfonyurea-tolerant canola in 2015. This product, developed using genome-editing tools, did not require FDA approval. Traits that seem to be amenable for genome-editing approaches include herbicide tolerance, improved oil content, resistance to bacterial and fungal pathogens and crops with more nutritional value, fewer allergens and longer shelf life.

The regulatory status of genome-edited crops is shown in the table below.

TABLE 53

REGULATORY STATUS OF GENOME-EDITIED CROPS

Parameter	U.S.	Europe
Overal approach	Case-by-case	Uncertain
Regulatory trigger	Does the crop contain foreign DNA?	Could the genetic alteration arise from natural recombination?

Source: BCC Research

The U.S. and Europe are taking different approaches to regulating genome-edited crops. In the U.S., the regulatory requirements for several agricultural crops modified via genome editing have been waived by the FDA. It is likely that the FDA will continue to evaluate these new products on a case-by-case basis. The main factor determining if regulations apply is if the crop contains foreign DNA or not. Since the methods using genome editing do not introduce foreign DNA from another species into the species' genome but use only genetic material from the organism's own genome, these products would not be considered GMOs.

In the E.U., the situation is still evolving, and it appears that the E.U. is more concerned with whether or not the genetic change could occur from natural recombination in applying regulations to these products.

The main applications for genome-edited animals include beef, dairy and porcine.

The market for genome-edited animal products is being driven by a growing demand for animal protein. By 2030, the global population is expected to increase by 1 billion and the proportion of urbanized populations will increase from 54% to 60% of the total. Urbanized populations have higher demand for animal protein because they are wealthier than urban populations.

The two main market segments for animals include porcine and dairy/beef. The porcine market has high barriers to entry and strong product differentiation. In contrast, the beef/dairy market has lower barriers to entry and less product differentiation.

DNA STORAGE APPLICATIONS

Today's information storage media have finite self life, requiring that the servers and hard drives be replaced periodically. This transfer increases the risk of data corruption and loss.

Synthetic DNA has great promise as data storage medium, as DNA has been shown to be stable for thousands of years. Information storage methods are being outstripped by the amount of data that is being generated. DNA is the most dense archival storage media available. Proof of concept for using DNA for data storage has been demonstrated by a

leader in this field, Microsoft.[5] The authors demonstrated the feasibility of using DNA to archive data using 151 kB of synthesized DNA.

The two main advantages that DNA may provide for long-term data storage are increased density and long-term durability.

The cloud and data center storage market is growing at more than 10% per year, driven by applications in cloud computing and online video content, such as Netflix, YouTube and video in social media. The need for increasing storage capacity is also being driven by big data analytics, the growth of the internet and strong demand for co-location and off-premise managed services.

While the long-term possibilities for DNA storage are promising, commercialization is expected to fall outside of the five-year time frame of this report.

[5] Bornholt et al., A DNA-based archival storage system, in: ASPLOS '16, April 2–6, 2016, Atlanta, GA; pp 637–49.

Chapter 6

SYNTHETIC-BIOLOGY INDUSTRY

SYNTHETIC BIOLOGY: GLOBAL MARKETS

BIO066D
January 2017

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ISBN: 1-62296-433-0

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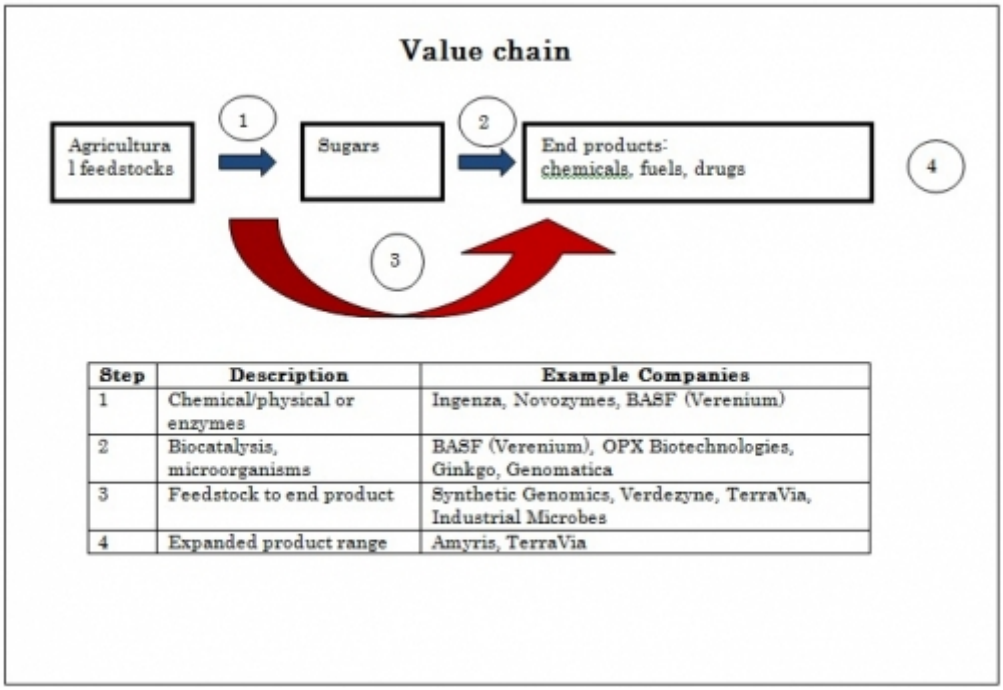
CHAPTER 6
SYNTHETIC-BIOLOGY INDUSTRY

INDUSTRIAL BIOTECHNOLOGY VALUE CHAIN

The figure below shows how synthetic-biology tools impact the industrial biotechnology value chain.

FIGURE 9

INDUSTRIAL BIOTECHNOLOGY VALUE CHAIN WITH SYNTHETIC BIOLOGY LEVERAGE POINTS



Step	Description	Example Companies
1	Chemical/physical or enzymes	Ingenza, Novozymes, BASF (Verenium)
2	Biocatalysis, microorganisms	BASF (Verenium), OPX Biotechnologies, Ginkgo, Genomatica
3	Feedstock to end product	Synthetic Genomics, Verdezyne, TerraVia, Industrial Microbes
4	Expanded product range	Amyris, TerraVia

Source: BCC Research

Conversion of agricultural products or by-products to simple sugars is the first step in the production process. This step may include chemical or physical pretreatment of the agricultural feedstock, particularly if it is cellulosic biomass. Conversion into simple sugars is accomplished by specific microorganisms that are engineered for this task. Agriculture feedstock choices may be expanded depending on the capability of these microorganisms. For example, cellulosic biomass may be a viable feedstock choice as a result of engineered microorganisms that can breakdown the cellulosic matter and convert it to simple sugars. The first leverage point for synthetic biology is creating unique microorganisms or enzymes that can utilize a wider variety of biomass feedstocks.

In the second step of the value chain, simple sugars are converted into a variety of products such as chemicals, fuels, pharmaceuticals or materials. Fermentation technologies are important in this step, and synthetic-biology tools can be used to provide better microorganisms for converting at higher yields and more economically.

Synthetic-biology-enabled technologies may also allow steps (1) and (2) to be combined into one step, for example, by going from cellulosic matter directly to the final product (bypassing the sugar-to-final product step). Some of the synthetic-biology companies pursuing this strategy are shown in the figure. The advantage is potentially significant cost savings by eliminating process steps.

Synthetic biology may also impact the end-product range that is possible using bioprocessing (step 4 in the figure). This strategy goes beyond the conventional fermentation route to ethanol or biodiesel products.

For example, TerraVia is producing a range of oils for skin-care, cosmetics, lubricants and food ingredients.

Amyris is producing jet fuels and isoprenoid specialty compounds.

An expanded product range increases significantly the value added of a given bioprocess.

INDUSTRY STRUCTURAL FORCES

The competitive forces in the synthetic-biology industry are analyzed in the table below. The analysis is based on the classic Porter model of structural industry analysis. We examined the barriers to entry, threat of substitute products and the bargaining power of suppliers and customers to determine the forces driving industry competition in each industry segment.

TABLE 54

SYNTHETIC-BIOLOGY INDUSTRY STRUCTURAL FORCES

Industry Segment	Number of Producers/Competitive Intensity	Threat of New Entrants	Technology Substitutes	Power of Suppliers	Power of Buyers
Enabling technologies	Many/high	High	High	Low	Low
Biologic components	Few/Moderate	Moderate	Low	Low	Moderate
Integrated systems	Few/low	High	Low	High	Low
Enabled products	Few/high	Low	Low	High	High

Source: BCC Research

The enabling technologies industry segment (e.g., DNA sequencing, DNA synthesis, bioinformatics, genome editing, microfluidics, etc.) is characterized by multiple technologies, many producers and high competitive intensity. The threat of new entrants is high because rapid technology change creates opportunities for new companies to enter the market (e.g., Gen9 and Twist Bioscience in DNA synthesis and multiple companies in

genome editing). Likewise, the threat of substitute technologies is high in these market segments (e.g., next-generation DNA synthesis, cluttered regularly interspaced short palindromic repeats (CRISPR)/Cas9 in genome editing).

The bargaining power of buyers is low because producers face high switching costs (e.g., the high price of DNA-sequencing instruments lock in a user for several years); the products do not represent a large fraction of the buyer's costs; and buyers do not pose a credible threat of backward integration (e.g., home-brew methods are the principal alternative).

The bargaining power of suppliers (i.e., reagents, instrument components) is also low because they do not pose a credible threat of forward integration into the DNA-sequencing or oligonucleotide-supply businesses, and the suppliers selling to the industry are more fragmented than the buyers (DNA-sequencing and oligonucleotides companies). These structural forces drive this industry toward high competitive intensity, with multiple producers. High competitive intensity creates a favorable situation for synthetic biology: it drives down the costs of DNA sequencing and synthesis.

The biologic components (e.g., synthetic genes, BioBrick parts) industry segment has moderate competitive intensity, and the industry is less fragmented than enabling technologies. The threat of new entrants is moderating in this industry, as evidenced by a reduction in the number of synthetic-gene companies during the past seven years. Product differentiation in the form of gene-synthesis design services, as well as scale economies (derived from in-house sourcing of a key raw material – oligonucleotide [oligos]), are helping to create entry barriers. The pressure from substitute technologies such as polymerase chain reaction cloning is decreasing as the cost of synthetic genes and other DNA parts decreases, and their usefulness to researchers increases.

The bargaining power of suppliers (e.g., oligo manufacturers) is low because they pose a declining threat of forward integration into the gene-synthesis business and their products are not differentiated. The bargaining power of buyers (government and academic laboratories, pharmaceutical, chemical and energy companies) is moderate. Buyers pose no credible threat of backward integrating into the gene-synthesis business, and the synthetic-gene products that they purchase are differentiated and important to the quality of the buyers' products. These factors act to decrease buyers' bargaining power. Buyers do make large volume purchases relative to suppliers' sales, which increases buyers' bargaining power.

These forces have contributed to a net reduction in industry fragmentation, resulting in a relatively few top-tier suppliers of biologic parts in the industry.

The integrated systems industry (suppliers of organisms with minimal genomes, synthetic chromosomes or genomes) is emerging, with few existing competitors. The threat of new entrants is high, due to the rapid development of new technologies. The threat of technology substitutes is low because there are as yet no entrenched technologies in this industry. The bargaining power of suppliers (synthetic genes) is high as synthetic genes are an important input to this business, and the integrated systems industry is not yet an important part of the suppliers' business portfolio. The bargaining power of buyers (laboratories) is low since they pose no threat of backward integration, the products (minimal genomes) are highly differentiated and the products' quality is important to the

buyer. Since the power of suppliers to this industry is high, and suppliers (synthetic-gene companies) will want to increase their business opportunities over time, there is a future likelihood that some synthetic-gene companies may acquire technology or otherwise seek to participate in the integrated systems business.

The enabled products industry segment (e.g., pharmaceuticals, chemicals and agriculture) has few producers, with high competitive intensity. The threat of new entrants is low due to high economies of scale, capital requirements, switching costs and access to distribution channels. The threat of technology substitutes is also low because, once a synthetic biology bioprocess is adapted by a factory, it is very difficult and expensive to switch to a new process due to regulatory, validation and capital requirements. The bargaining power of suppliers (i.e., companies providing renewable feedstocks, enzymes, etc.) in the industry is high. Raw material feedstocks are a critical supply input to the industry, and once a feedstock is decided, it is difficult to switch to another source. For this reason, several companies have formed alliances with feedstock and enzyme suppliers to secure access to these inputs. The bargaining power of buyers is also high, since the products they purchase (specialty chemicals, biofuels) are undifferentiated and the buyer can easily find another source if necessary. These industry forces result in relatively few competitors limited to the large chemicals and pharmaceuticals companies. However, the competitive intensity is high due to the power of suppliers and buyers. Synthetic biology allows the competitors to reduce their production costs to compete better in this industry environment.

PRODUCTS AND TECHNOLOGY LIFE CYCLE

The table below shows the life-cycle stage of principal synthetic-biology products and technologies. Enabling technologies, including DNA synthesis and sequencing, are rapidly maturing. Next-generation sequencing (NGS), first introduced in 2005, is rapidly maturing. Oligonucleotide synthesis is also a mature technology.

For enabling technologies, there are two potentially disruptive technologies on the horizon: nanopore sequencing and chip-based DNA synthesis. As these platforms are developed and introduced in the industry, the life-cycle stage will revert to an emerging–mature situation.

TABLE 55

SYNTHETIC--BIOLOGY PRODUCTS AND TECHNOLOGY LIFE-CYCLE STAGE

Product Category	Principal Technologies	Life-Cycle Stage		
		Embryonic	Emerging	Mature
Enabling technologies	DNA synthesis; DNA sequencing; genome editing		X	X
Biologic parts	Gene synthesis; biologic parts		X	
Integrated systems	Minimal genomes; synthetic cells	X		
Enabled products	Bioprocesses		X	

Source: BCC Research

Biologic parts including synthetic genes and regulator parts may be considered as emerging products and technologies. Technology for making synthetic genes is rapidly maturing, particularly for standard genes (short length, low guanine–cytosine [GC] content, etc.). However, for many complex genes and long DNA constructs, the technology is still emerging. In addition, biologic parts such as genetic regulatory switches are still emerging.

Integrated systems (synthetic and minimal genomes, synthetic cells) are the most embryonic synthetic-biology products and technologies. The first synthetic genome was created in January 2008, and much technical work still needs to be done before commercial products emerge. Synthetic cells are even farther away from commercialization.

Enabled technologies and products may be considered as emerging if we look only at the synthetic-biology component of such technologies. This is usually a highly engineered microorganism designed with a particular feedstock and end product to be produced. If we are considering the end products, such as ethanol or a specialty chemical, these are at a mature life-cycle stage.

The conclusions we can draw about the life-cycle situation in synthetic biology reflect the diversity of this field: products and technologies span the life-cycle stages from embryonic to mature. The implication for companies is that, in order to be major players in synthetic biology, both high technical and commercial implementation skills are required. For example, in the chemicals application space, successful companies must know how to apply both synthetic-biology tools together with chemical engineering tools in order to successfully start-up a bioprocessing plant. This gives an advantage to diversified companies with deep technology skills such as DuPont, while other companies may need to partner to successfully implement a process.

Industry sectors analyzed in the following sections include DNA sequencing, DNA synthesis, genome editing, synthetic-biology foundries, industrial biotechnology, pharmaceuticals and agriculture.

DNA-SEQUENCING INSTRUMENT INDUSTRY

The main NGS instrument companies are listed in the following table.

TABLE 56

NEXT-GENERATION SEQUENCING INSTRUMENT COMPANIES SUMMARY

Company	Commercial Summary	High-Throughput Instrument	Desktop Instrument
Illumina	Overall market leader in high-throughput and benchtop sequencers; aggressively pursuing clinical applications and alliances	HiSeq	MiSeq, NextSeq, MiniSeq

Thermo Fisher Scientific	Focus is in the benchtop market segment	SOLiD	PGM, Ion Proton
Pacific Biosciences	Creating a niche position in long-read sequencing	RSII	NA
Qiagen	Recent launch of instrument system targeted to clinical applications	None	GeneReader
Oxford Nanopore	Early phases of launch for a handheld sequencer	None	MinIon

NA, not applicable.

Source: BCC Research

Illumina is the leader in this industry, with an estimated 75% share of the overall NGS instrument market.

In the high-throughput sequencing instrument segment, Illumina is particularly dominant, accounting for more than 90% of the global sequenced genetic material. Illumina has achieved this position at the expense of Thermo Fisher's SOLiD and Roche's GS FLX instrument platforms, creating a near monopoly in this market segment.

In the benchtop sequencer segment, Illumina sees more competition from Thermo Fisher, but still has a market share of more than 50%. The benchtop market segment is particularly important in clinical applications.

Illumina's main platforms in the high-throughput market segment are the HiSeq 2500, 3000 and 4000 instruments, and the HiSeq X Ten and X Five instruments.

Illumina's main platforms in the benchtop market segment are the MiSeq, MiSeqDx, MiniSeq and the NextSeq 550 instruments.

Illumina maintains its market position by technology innovation and strategic initiatives. The company's instruments are extremely versatile and they perform well versus the competition on key parameters including sample preparation time, run costs, turnaround time, read lengths, throughput and error rates. Most importantly, Illumina provides the full range of NGS workflow tools, including front-end sample preparation products and back-end cloud based data storage and data analysis software.

Complementing its technology strategies, Illumina has aggressively pursued large and growing markets including clinical applications. A key part of this strategy is forming a network of alliances and subsidiary companies that can help Illumina achieve its goals in the clinical market.

Since 2013, Illumina has acquired the following companies: Moleculo (conversion of short reads into longer reads), Verinata Health (noninvasive prenatal test diagnostics), Advanced Liquid Logic (digital microfluidics), and Myraqa (clinical diagnostics regulatory consulting firm). During that same time, Illumina has formed strategic alliances with the following companies: SynapDx (autism spectrum disorder diagnostics), Kindstar Global (China diagnostics laboratory), bioMérieux (infectious diseases), AstraZeneca, Janssen Biotech, Sanofi, Amgen (companion diagnostics), and Merck Serono (cancer diagnostics),

Illumina’s competitive position in the sequencing industry is enhanced by the growing barriers to customer switching. As the market leader, Illumina will benefit from this trend. Switching costs arise when customers coalesce around a specific laboratory workflow, which then becomes entrenched and difficult for competitors to overcome. The workflow includes sample preparation procedures, quality control, and data analysis and storage methods. A second switching cost in the clinical market is a reliance on peer-reviewed medical publications for a particular sequencing platform. Clinical laboratories in particular often do not have the technical expertise or the resources to run diagnostic tests on more than one platform, once a particular protocol has been established.

U.S. Food and Drug Administration (FDA) approval of the sequencing instrument platform is also a key clinical industry strategy. Illumina’s MiSeq was the first FDA-approved genome-sequencing instrument, and the company is pursuing approval for its NiSeq and NextSeq instruments. Thermo Fisher also recognized the importance of getting approval and followed Illumina with approval of its Ion Torrent PGM Dx system.

Thermo Fisher Scientific occupies the position of being the main alternative to Illumina among clinical and other sequencing customers. With its acquisition of Life Technologies in 2014, Thermo Fisher acquired the SOLiD and Ion Torrent instrument platforms. As discussed above, the SOLiD platform has been almost completely overtaken by Illumina’s HiSeq instruments. However, Thermo Fisher is still competitive in the benchtop market segment with its Ion Torrent PGM and Ion Proton platforms.

These systems use semiconductor chips that contain sensors to detect protons given off during nucleotide addition. The main advantages of this approach include the use of unmodified nucleotides and easy scale-up of the detection system. The PGM system is marketed to the diagnostic industry for targeted applications and individual gene analysis. The Ion Torrent instrument has been well accepted, but it must overcome a perception of lower-quality data.

MiSeq, Illumina’s benchtop platform, competes with the PGM instrument. MiSeq is a more-expensive instrument, and it is slower than the PGM, but it is thought to be better in data accuracy, particularly in reading homopolymers (i.e., regions of DNA where a given sequence is repeated many times and that are prone to insertions or deletions). MiSeq is a preferred platform from a quality standpoint, which will help its future growth.

MiniSeq is about 50% smaller than the MiSeq instrument. This benchtop instrument was launched in January 2016 and targets the low-priced, low-throughput portion of the benchtop market. Key customer groups include smaller laboratories, molecular pathologists and clinical researchers.

From its second-place market position, Thermo Fisher has been aggressive in the clinical-sequencing market segment. The company obtained the European CE-IVD marking and FDA approval for its Ion PGM Dx system, helping with its penetration among clinical laboratories.

Thermo Fisher, like Illumina, is trying to offer complete NGS workflow options to its clinical customers. An example is its January 2015 strategic alliance with Cynevio for liquid biopsy cancer diagnostics applications. The partners will offer circulating tumor cell isolation

technology (LiquidBiopsy), NGS sample preparation (Ion Chef), sequencing (Ion Torrent PGM) and hot-spot analysis (AmpliSeq) as a complete workflow to customers.

Thermo Fisher is seeking to become a supplier to the universal oncology companion diagnostics market, as evidenced by its 2014 alliances with GlaxoSmithKline and Pfizer. Success with these projects could provide a strong boost to Thermo Fisher's future clinical NGS business.

Pacific Biosciences is a niche competitor in the NGS instrument industry, with its single-molecule, long-read platform. The company has a very low, single-digit market share in the overall NGS instrument market and is not in the clinical-sequencing market. The main applications for Pacific Bioscience's RSII instrument have been in bacterial and microbial genome sequencing.

Pacific Biosciences has a strategic alliance with Roche covering the development of clinical applications, but the company is still in the development stage and has not launched any commercial systems.

Roche/454 was the first company to launch commercial NGS instruments in 2005. Roche's instruments are known for their longer read lengths and high-quality sequence data.

Roche's position in NGS with its 454 sequencing platform began declining in 2012, and the declines only accelerated since then, due to strong competition from Illumina's MiSeq and Ion Torrent's Ion Proton platforms. In October 2013, Roche began exiting its 454 sequencing business; this exit was completed in 2016.

In addition to Illumina, Thermo Fisher and Pacific Biosciences that offer commercial instruments, there are several companies developing advanced, third-generation, sequencing instrument platforms. These companies include Bio-Rad Laboratories (GnuBIO), GenapSys, Lasergen, Oxford Nanopore Technologies (MinIon), Qiagen (Intelligent Biosystems), QuantumDx and Roche (Genia and Strator Genomics).

Of note is the recent launch of GeneReader by Qiagen in November 2015. GeneReader is a benchtop NGS system marketed as a sample-to-sight system. The instrument system is targeted for clinical NGS workflows.

In September 2016, a U.S. federal court issued a preliminary injunction against Qiagen, which stopped the sale of its GeneReader sequencing instrument in the U.S. In June 2016, Illumina had sued Qiagen for patent infringement, alleging that the GeneReader instrument violates a patent Illumina holds covering sequencing by synthesis technology. As of January 2017, the preliminary injunction is under review by the U.S. Court of Appeals for the Federal Circuit.

The likely outcome of this issue is that Qiagen may need to modify its sequencing chemistry and use a different blocker to slow the sequencing process. This process will take some time as any change to its method would also have to be validated, thus pushing out the sales of GeneReader in the U.S. until mid-2017.

Oxford Nanopore is marketing its MinIon sequencer to the handheld market, which is a new segment for sequencing. MinIon is a nanopore-based sequencing platform, and is still

in the early phases of its commercial launch. Its handheld size means that this system could see large applications in education and point of care applications.

THIRD-GENERATION SEQUENCING INDUSTRY

The third-generation sequencing (3GS) industry is important to the future growth of the overall sequencing business. 3GS companies focus on single-molecule technologies that often involve nanopores. The commercial introduction of these platforms has been slow to develop, as NGS systems are firmly entrenched with end users.

As a result, for some 3GS formats, niche applications are the first entry point into the industry.

The table below summarizes this industry, including the technology approach and relative technical and commercial strength of each company.

TABLE 57

THIRD-GENERATION SEQUENCING INDUSTRY

Company	Platform	Stage	Technical Strength	Commercial Strength	Tier Status
Base4/ Hitachi	Solid-state nanopore, unique read system	Initial feasibility	High	High	Tier 3
Electronic BioSciences	Protein nanopore	Early concept	Low	Low	Tier 3
Electron Optica – no longer a player	Electron microscopy imaging	Early concept	Moderate	Low	Tier 3
GenapSys	Biochip, label-free detection	Early concept	Moderate	Low	Tier 2 (due to Sigma Aldrich alliance)
Genia (acquired by Roche)	Tag-based, protein nanopore	Distinguish bases	High	Moderate	Tier 1
GnuBIO (BioRad acquired in 2014)	Microfluidics, sequencing by hybridization	Beta test	High	Moderate	Tier 1
Illumina	Protein nanopore	Sequencing feasibility	High	High	Tier 1
Oxford Nanopore	Protein nanopore	Early access	High	Moderate	Tier 1
Pacific Biosciences	Protein nanopore	Commercial	High	High	Tier 1

Stratos Genomics	Sequencing by expansion, solid-state nanopore detection	Sequencing feasibility	Low	Low	Tier 2 (due to Roche alliance)
Two Pore Guys	Sequencing through two solid-state nanopores	Early concept	Moderate	Low	Tier 3
ZS Genetics	Electron microscopy imaging	Distinguish bases	Low	Low	Tier 3

Source: BCC Research

The 3GS industry has been characterized by numerous start-ups and technologies, as well as by a very long development and commercialization time. Several companies that were in this industry several years ago are no longer in the business, including NobleGen Biosciences, Electron Optica, NabSys and Helicos.

Companies in this industry can be segregated into three tiers. Tier 1 companies have strong technologies and business models and are often associated with larger, established companies. Tier 2 companies have promising technologies and moderately strong business models (e.g., an alliance with an established company). Tier 3 companies have early-stage technologies and weaker business models.

Tier 1 companies include Pacific Biosciences, Oxford Nanopore, Roche (Genia), Bio-Rad (GnuBIO) and Illumina. These are the leaders in the 3GS market.

Pacific Biosciences is a leader in 3GS, with strong commercial sales and alliances. In 2013, the company formed a partnership with Roche to codevelop diagnostic products for the Pacific Biosciences instrument. In October 2015, the company launched the Sequel System, developed as part of its partnership with Roche. The Sequel sequencer uses single-molecule real-time sequencing technology and has an enhanced optical system that allows the instrument to have a smaller footprint than the RS II sequencer.

Pacific Biosciences is moving rapidly down the technical and commercial learning curves, is well funded, and thus presents a very strong competitor in this industry.

In May 2015, Oxford Nanopore, a leader in nanopore-based sequencing technology, began making its MinIon handheld sequencer commercially available to early-access customers. The company had been slow to develop its sequencer technology, but during 2015 it seemed to make significant progress on the commercial front.

Illumina is a leader in the NGS industry, and in January 2016 released a new benchtop sequencer, MiniSeq. MiniSeq is based on Illumina’s current sequencing technology. Illumina has a high stake in maintaining the NGS format for as long as possible, as it leads this industry. However, the company has made several moves in nanopore sequencing as a hedge in case this technology began to supplant current NGS formats.

In October 2013, Illumina finalized a licensing agreement with the University of Alabama–Birmingham covering the global, exclusive rights to nanopore-sequencing technology developed at the university. In January 2013, Illumina acquired Moleculo, giving Illumina a way to increase the read length of its sequencing-by-synthesis platforms.

These moves, made several years ago, helped Illumina to still be a factor in the long-read 3GS business, as it developed in the future. However, during the past several years, Illumina seems to have focused on strengthening its NGS benchtop platforms to help preempt encroachment by the newer technologies into the company's market space.

In April 2014, Bio-Rad acquired GnuBIO, which was developing a novel sequencing technology based on microfluidics. Since that time, Bio-Rad has invested in further developing this system, but has yet to announce a launch.

In June 2014, Roche acquired Genia Technologies, which was developing a single-molecule sequencing technology with nanopore-based electrical detection and integrated circuit components. At the time, this acquisition fit within Roche's plan to develop a novel sequencing workflow; however, the company has yet to announce a product launch.

Tier 2 companies include GenapSys and Stratos Genomics.

GenapSys Inc. is an early-stage company that is developing a sequencing system that avoids optical detection by using nanosensor arrays. The company strengthened its platform viability when it formed an alliance with Sigma Aldrich in July 2015. Sigma Aldrich agreed to market the Genium sequencing system through its marketing channels.

Stratos Genomics is developing a single-molecule sequencing system based on proprietary nucleotides; the system uses nanopores for the sequencing step. Roche made a significant investment in Stratos in June 2014 and an additional milestone payment in June 2015 after the nanopore-sequencing platform met certain criteria. This alliance with Roche adds significant viability to Stratos' business model.

Tier 3 companies include Base4/Hitachi, Electronic BioSciences, Two Pore Guys and ZS Genetics.

These companies are developing novel sequencing technology, but have a weaker business model, with no major strategic alliances or product launches after long development periods.

OLIGONUCLEOTIDE SYNTHESIS INDUSTRY

DNA synthesis consists of single-stranded DNA (oligos) and double-stranded DNA (genes). The industries are closely related to each other, and many companies are in both of these markets. The estimated market shares for the oligo synthesis industry are shown in the table below. Total market size is estimated to be $268.4 million in 2016.

TABLE 58

GLOBAL MARKET SHARES OF OLIGONUCLEOTIDE SYNTHESIS INDUSTRY, BY COMPANY, 2016
($ MILLIONS/%)

Company	Revenue ($ Millions)	Share (%)
Thermo Fisher Scientific	59.3	22.1
Integrated DNA Technologies	52.3	19.5
Bioneer	23.6	8.8
Sigma Aldrich	16.1	6.0
Agilent Technologies	10.5	3.9
Other	106.6	39.7
Total	268.4	100.0

Source: BCC Research

The top five producers in this market account for an estimated 60.3% of the 2016 market on a revenue basis. The oligo synthesis market is quite competitive and fragmented, as there are many smaller competitors outside the top five producers.

The market share leaders have established a competitive advantage by offering fast delivery of high-quality products on a global basis.

Thermo Fisher Scientific is a global life sciences reagents and kits company, with strong distribution to the major user communities. Products include DNA sequencing, oligo and gene synthesis, cell culture media and bioinformatics.

Integrated DNA Technologies is a leading supplier of custom oligonucleotides as well as genomics and molecular-biology tools. The company is among the top tier of global synthetic DNA suppliers.

Bioneer, located in Asia, supplies a range of life science reagents and kits, including for molecular diagnostics, gene therapy, genetic engineering and DNA synthesis.

Sigma Aldrich offers on a global basis an extensive range of chemicals and life science reagents and kits to the research market.

Agilent Technologies is a developer and marketer of life science research tools, and it has a comprehensive service and product portfolio, which includes DNA synthesis and sequencing, protein expression and purification, cell cultivation and transfection and a range of reagent kits.

Several companies are using high-density microarray technologies for producing oligos, which can then be assembled into genes. These companies include Agilent Technologies, Gen9 and Twist Bioscience.

GENE-SYNTHESIS INDUSTRY

WORKFLOW

The typical workflow, from ordering to shipping, for synthetic genes or long DNA constructs is shown in the table below.

TABLE 59

GENE-SYNTHESIS WORKFLOW

Step	Description
Customer orders sequence	Ordered via email or secure website
Sequence optimization	Software to optimize DNA sequence for use in host system
Gene synthesis	Assembly of oligo fragments into long DNA construct
Cloning	Insertion of gene into plasmid
Sequence verification	Quality control using sequencing
DNA shipped to customer	Customer receives the exact sequence ordered

oligo, oligonucleotide.

Source: BCC Research

Gene companies need to take their orders by email or through their websites. Since the length of the sequence is large, it is not feasible to take orders by phone or fax.

For many orders, it is necessary to optimize the gene sequence from the customer. This is done using proprietary algorithms that consider factors such as GC content, codon usage, messenger RNA (mRNA) folding and so forth to produce the most optimal sequence for expression in the desired host system.

Gene optimization software is a source of competitive differentiation among gene-synthesis companies. There are no widely used software packages available to the industry, and so most gene-synthesis firms have developed their own internal software. Those open-source programs that are freely available (e.g., at the website www.evolvingcode.net/codon/, there are over 35 packages listed) are less sophisticated and efficient than those developed by the gene-synthesis companies.

A key component of these software packages is codon optimization. Since many synthetic genes are used for protein expression, and codon usage differs among species, codon optimization becomes critical. For example, *Homo sapiens* use the genetic code AGA and AGG for arginine with a 21% frequency, while *Escherichia coli* uses the same codons at only 2% to 4% frequency. As a result, in heterologous expression systems where a human gene is expressed in *E. coli*, the concentration of transfer RNAs for the codons AGA and AGG is low, and protein expression is inefficient. Software packages that can automatically adjust the coding sequence for the codon usage of the host organism (so that the codon frequency matches the host organism) are a key tool.

Additional features of optimization software include avoidance of direct and inverted repeats and hairpins, even distribution of GC content, incorporation of good motifs, incorporation of organelle trafficking signals (to ensure trafficking to desired location), removal of degradation signals (to increase mRNA stability) and removal of protein functional domains. The design of the DNA sequence to optimize protein expression, function or stability is a main differentiating factor for competitors.

Gene synthesis involving assembly of many oligo fragments is a key step in the overall workflow. The gene-synthesis process has become automated in order to keep costs low. Each synthetic-gene product has a unique sequence, which presents unique production challenges. The successful synthetic-gene company must be efficient with mass customization–automated production of individual products that are different.

After assembly, synthetic genes are cloned into a vector of choice (either a publicly available vector or the customers' own vector) and then quality controlled to verify the fidelity of the DNA sequence. Quality control is done using DNA-sequencing technologies. The genes are shipped as a purified plasma DNA with a bacterial strain containing the plasmid.

The final step is packaging the DNA and shipping it to the customer. The entire gene-synthesis process may take from one to four weeks, depending on the complexity of the order.

As seen from this workflow description, gene synthesis is quite complex compared with oligo manufacturing. Unlike oligos, in gene synthesis the initial DNA sequence design is much more significant, and every order is unique. In addition, many component chemical parts (oligos) are used (up to several thousand), chemical parts may contain errors that must be identified and corrected and the final sequence must be error free. This increased complexity of design and production workflow means that gene synthesis requires additional skills beyond what a typical oligo manufacturer can provide. This is one reason that only a few companies now dominate the synthetic-gene industry, while the oligo industry is very fragmented with large numbers of suppliers.

Synthetic-gene companies can gain competitive advantage through manufacturing know-how and efficiency. The ability to adequately deal with the unique requirements of gene synthesis – mass customization (many orders, each one of which is different), automation and high oligo failure rates – will differentiate each company in this market.

COMPETITORS

The gene-synthesis industry is fragmented, with more than 30 companies offering some sort of gene-synthesis product. However, the industry is consolidating due to the rapid decline in gene-synthesis costs and the requirement for increasingly sophisticated automated manufacturing and sequencing quality control. Much gene synthesis is carried out today in sophisticated laboratories using some automation and highly skilled labor. However, the industry is moving toward automated plants with robotic processes, and sophisticated process control and scheduling. The main competitors will employ mix of technologies to allow synthesis of all DNA sequences desired by customers, and production will occur in centralized locations.

Estimated market share for the synthetic-gene industry is shown in the table below. Total market size is estimated at $200.2 million for 2016.

TABLE 60

GLOBAL MARKET SHARES OF GENE-SYNTHESIS INDUSTRY, BY COMPANY, 2016 ($ MILLIONS/%)

Company	Revenue ($ Millions)	Share (%)
GeneScript	46.3	23.1
Integrated DNA Technologies	41.0	20.5
Thermo Fisher Scientific	22.8	11.4
Origene	19.6	9.8
ATUM	8.4	4.2
Others	62.1	31.0
Total	200.2	100.0

Source: BCC Research

The five leading companies have an estimated 69% share of this market. This concentration is mainly due to high entry barriers in this market segment. Entry barriers include technology, global distribution channels, strong brand recognition and high-quality scientific personnel.

The leading suppliers in this market segment include GenScript, Integrated DNA Technologies, Thermo Fisher Scientific, Origene and ATUM.

The remaining 31% of the market is highly fragmented. Companies in this 31% of the market are primarily molecular-biology tool providers, with a focus on genomic or proteomic products and services, and they may consider synthetic genes of long DNA sequences as a specialty portion of their oligo business.

Key factors differentiate gene-synthesis companies from oligo suppliers (which also provide long DNA). Gene-synthesis companies participate in a significant portion of the bioproduction value chain and therefore provide high-margin, value-added products and services. They have a higher emphasis on optimizing codons within the gene to increase protein production efficiency in host organisms. There is a focus on the quality of the synthesis product itself (the expressed protein). Finally, there is a higher level of design and consulting services to assist customers in using the synthetic gene in their projects.

Gene-synthesis companies often have experts in protein expression on staff who can consult with customers on particular projects.

The leading gene-synthesis companies have a competitive advantage of high brand reputation and name recognition among customers. Key customer groups that use synthetic genes include large pharma, biotechnology and academia. Any given customer

will typically only use one to two manufacturers, and this limits the opportunity for second-tier competitors to gain market share.

The number of companies in the top tier of the gene-synthesis market has consolidated from approximately 30 in 2000 to five in 2016. One of the factors for this shift has been a steady reduction in prices for synthetic genes. The average market price for gene-length DNA is reducing by a factor of two approximately every 18 months, and in 2016, this is less than $0.17 per nucleotide. Lower pricing is increasing the outsourcing among customers, total demand for optimized synthetic genes and growth in the market.

In this environment, the ability to reduce production costs (through automation, miniaturization and economies of scale) is a critical factor for success. Cost flexibility allows companies to compete in differentiated market segments including automated standardized genes (price sensitive), long DNA, gene clusters and whole genomes (low price sensitivity).

Gene-synthesis companies are investing in process and technology improvements, which have further accelerated the industry consolidation process.

Several suppliers have a high market share based on sales rather than volume sold, and these companies are able to attract premium prices for their products. These companies tend to specialize in making difficult-to-synthesize genes based on such factors as length, GC content or folding. Thermo Fisher Scientific (GeneArt) is a leading example of this strategy. This company has solidified its reputation and position in the high-end gene-synthesis market by taking orders for complex genes that cannot be made by conventional cloning technologies.

Companies with sales share lower than volume share may seek to use their share position to increase the pricing of their products.

The table below contrasts strategies of the top five gene-synthesis companies as well as several other companies.

TABLE 61

GENE-SYNTHESIS KEY COMPETITOR STRATEGIES

Company	Technology	Principal Competitive Strategy
Bio Basic Inc.	PCR assembly	Leverage its oligo synthesis, DNA sequencing and large customer base in gene synthesis
Bioneer	PCR assembly	Leverage its oligo synthesis and PCR tools in gene synthesis
ATUM	Various	Network of strategic alliances to leverage core synthetic-biology technology

Eurofins MWG Operon	Ligase-chain-reaction and PCR	Emphasizes value-added gene products with advanced codon-optimizing software and gene-variant libraries; key acquisition of Entelechon GmbH in 2013 enhanced market position
Gen9	Microfluidics	Next-generation synthesis
GenScript Corp.	PCR assembly	End-to-end source of genomics and proteomics tools; market focus on drug-discovery and development customers
Integrated DNA Technologies	PCR assembly	Low-cost oligos capability; offers long-length DNA and gene assembly through alliance with SGI-DNA; regional focus in California biotechnology corridor
Themo Fisher Scientific	Hybridization of long linkable strand with short nonlinkable strands	Strong design capability; proprietary synthesis technology; pursue value-added applications of gene synthesis; wide range of DNA-synthesis tools
Origene Technologies	Solid-phase columns	Acquired by leading research tools company; lead in complex gene orders (e.g., Synthetic Genomics)
SGI-DNA	Gibson Assembly	Assembly of oligos into large, value-added DNA constructs; alliance with IDT

IDT, Integrated DNA Technologies; oligos, oligonucleotide; PCR, polymerase chain reaction.

Source: BCC Research

BioBasic has an extensive customer base from its supply of a wide range of biochemical products. The company is using this customer base and its in-house oligonucleotide and DNA-sequencing capabilities to gain a competitive advantage in the gene-synthesis industry. The company recently shifted its gene-synthesis strategy from an emphasis on OEM supply to direct supply for its existing laboratory customer base.

Gen9 is developing array-based DNA-synthesis methods. These next-generation synthesis platforms have the potential to significantly reduce the cost of producing large DNA constructs by several orders of magnitude below today’s cost.

ATUM (formerly DNA2.0) uses partnerships and alliances as a way to leverage its synthetic biology capabilities. ATUM is working with Aldevron and Pfenex to develop gene design and synthesis algorithms for insect cells and *Pseudomonas fluorescens* cultures, respectively.

Eurofins MWG Operon positions itself in the value-added-gene market segment, using codon-optimizing software and high-value gene libraries to differentiate its products. The company’s position in the industry was strengthened by its June 2013 acquisition of Entelechon GmbH.

GenScript is focused on providing an end-to-end workflow product to its customers, including both genomics and proteomics products. This allows GenScript to be a full service provider to its customers. Important tools that have been recently added include Gene–Brick gene synthesis (for customers that need large DNA fragments) and PROtential,

which allows customers to measure the protein-expression efficiency of their synthetic genes.

GenScript emphasizes large pharmaceutical firms and gene-synthesis technologies for improving drug discovery and development.

Integrated DNA Technologies is a large producer of oligos, which provides it a cost advantage in gene synthesis. The company has made acquisitions in California to enable better service to the life sciences industry in that region. Integrated DNA Technologies offers long-length DNA constructs (up to 2 Mbp [bp: base pairs] in length) through its alliance with SGI-DNA.

Two of the leading synthetic-gene companies – Thermo Fisher Scientific and Origene – have strong ties with the global life science tool companies by which they were acquired. This provides these companies with strong global distribution and marketing resources.

Origene uses solid-phase support strategy that allows for a fully automated, high-throughput gene-synthesis platform. The company's commercial strategy relies on partnering with Invitrogen for global distribution and marketing, and capturing orders for high-visibility, complex gene projects, including those with Synthetic Genomics.

Thermo Fisher Scientific possesses excellent gene-design capability and is fully integrated in the gene-synthesis value chain. The company is strong in all segments of the industry, and pursues value-added applications such as vaccines through its strategic partnerships. Thermo Fisher also has created multiple tools that enhance its synthesis services. These include genome editing, custom DNA fragments, gene cloning and assembly kits, premade clones, site-directed mutagenesis and directed evolution.

SGI-DNA specializes in sequence-verified genomic blocks, which can be assembled into larger DNA constructs using Gibson Assembly. SGI-DNA formed an alliance with IDT, which enhances the front-end oligo manufacturing, and the back-end marketing of synthetic-gene products.

VALUE CHAIN

The gene-synthesis value chain consists of the following:

- Gene design – optimization of the naturally occurring gene for its intended use. This is a critical component of gene design, and differentiates companies in the industry.
- Production of gene precursors: oligonucleotides – phosphoroamidites, oligo synthesis and purification. Integration in this step represents a significant core advantage to gene-synthesis companies, as they can control the cost and quality of their raw materials.
- Gene assembly – combining the oligonucleotides in the correct order to produce a custom-designed gene.

- Cloning – inserting the desired gene sequence into a plasmid for delivery.
- Quality assurance – DNA sequencing to ensure the correct nucleotide sequence.

Emphasis on different parts of the value chain provides access to specialized gene-synthesis market segments. For example, gene design and assembly emphasis allows a company to compete in the value-added, customized market segments of long DNA constructs, complex genes and whole genomes. On the other hand, integration into automated services allows companies to compete in the lower-cost, standardized gene-synthesis market segment. Customers in this segment are able to utilize a fully automated do-it-yourself approach to gene design, optimization and production.

Most of the top-tier gene-synthesis companies pursue a fully integrated strategy including oligo production. This allows maximum flexibility in raw material sourcing and costs for the gene-synthesis business. As a result, these companies can employ greater pricing flexibility in the low-cost, standardized gene market segments.

For example, Integrated DNA Technologies and Bioneer are leading global suppliers of oligos, and can thus use this advantage to achieve lower costs in their production of synthetic genes.

ATUM is one exception to this strategy among top-tier suppliers, and it sources its oligos from a leading supplier: Operon Biotechnologies.

GENE-SYNTHESIS MARKET SEGMENTS

Synthetic genes represent an attractive market for suppliers because they are enabling components of many research applications and are consumed in each experiment. Also, synthetic genes are custom products to each customer, and so the opportunity for differentiation is high. Synthetic genes represent a value-added opportunity for oligos suppliers that can adapt to this market segment. The market is rapidly maturing, and brand name, service and reputation for quality have become increasingly important to maintain market share.

There are three gene-synthesis market segments: automated standardized; value-added academic; and value-added industrial. Specialization in a given market segment allows gene-synthesis companies to differentiate and to maximize their market potential.

Standardized Segment

Automated standardized genes represent the low-cost market segment. In this segment, the customer typically orders one to 50 standard genes, and delivery time is critical. Typical order size ranges from $500 to $50,000.

Value-Added Segment

High-value-added market segments include two customer types: academic and industrial. High value added means long and often complex DNA components (e.g., large genes and functionalized gene clusters), specialty genes (e.g., RNA-interference-resistant genes) and whole genomes.

Academic customers demand larger constructs, often in the thousands of kilobases. Delivery time is not as critical to these customers. Industrial customers are time sensitive, and delivery is a purchasing factor. Length of DNA construct for industrial users is usually smaller than that of academic customers, in the hundreds of kilobase range.

The high-value-added market segments are strategically important to the development of synthetic-biology markets, as the DNA products are used in synthetic biology cell factories for producing biofuels or other products.

The table below describes factors that determine competitive advantage for gene-synthesis companies. Several factors are most useful in the value-added market segments, while other factors provide advantage in the standardized market segment.

TABLE 62

GENE-SYNTHESIS MARKET FACTORS OF DIFFERENTIATION

Factor	Description	Market Segments
Ease of submission	Can the customer easily submit sequences over the internet?	Standardized, value-added academic and industrial
Synthesis time	How fast can the gene be synthesized?	Standardized, value-added industrial
Insertion into customer vectors	Is the gene provided in a ready-to-use format?	Standardized
Availability of different gene forms (e.g., vectors)	Can the company provide any gene in any vector?	Value-added academic and industrial
Synthesis accuracy	Does the final sequence order match the design sequence?	Standardized, value-added academic and industrial
Synthesis options	Can the company provide both standard and complex genes?	Value-added academic
Assistance with gene design	Does the company have advanced gene-design capability?	Value-added industrial
IP protection	Are the gene-sequence motifs protected?	Value-added industrial

IP, intellectual property.

Source: BCC Research

Factors that are most important to the standardized market segment include ease of submission, synthesis time and insertion into customer vectors. Each of these factors

contributes to time and ease of use, which are important needs for customers using standard genes.

The ability to provide a wide range of genes and vectors is a competitive advantage, especially in the value-added market segment. The company should be able to synthesize any gene, subclone it into any destination vector and deliver it to the customer in a ready-to-use format.

Accurate gene synthesis is a prerequisite for all market segments and a critical factor. High-yield production methods, as well as accurate quality control using DNA sequencing, are important to achieving these quality goals.

Providing an efficient, effective gene design is another differentiating factor. Gene design includes codon optimization, mRNA secondary structure modification and other methods to increase gene expression. Proper gene design boosts gene-expression efficiency in host systems. This capability is particularly important in the value-added industrial segment where protein-expression efficiency is a critical parameter.

Intellectual property protection is important to the value-added industrial customers because they are most often working with more complex, proprietary sequences. This market segment also values flexibility in a supplier for providing both more complex and standardized genes.

GENOME-EDITING TOOLS INDUSTRY

Companies within the genome-editing tools industry are shown in the table below.

TABLE 63

GENOME-EDITING TOOLS INDUSTRY

Company	Market Focus	ZFN	TALEN	CRISPR/Cas9	Mega-Nuclease	Other
ATCC	Research			X		CRISPR tools
Bluebird bio	Pharmaceuticals		X			
B-MoGen Biotechnologies	Research			X		
Caribou Biosciences	Research, services, agriculture			X		
Cellectis	Agriculture, therapeutics		X		X	
Cellular Dynamics	Research	X	X			Cell model tools
Cibus	Agriculture					X
CRISPR Therapeutics	Therapeutics			X		

Dow AgroSciences	Agriculture	X			X	
DuPont	Agriculture			X		
Editas Medicine	Therapeutics			X		
eGenesis	Medical			X		
GE Healthcare	Research			X		CRISPR tools
Genus	Animal			X		
Horizon Discovery Group	Research, therapeutics	X		X		
Integrated DNA Technologies	Research			X		
NVS/Intellia Therapeutics	Therapeutics			X		
Plasticell	Research	X				ZFN tools
Precision BioSciences	Animal, agriculture, therapeutics					X
Recombinetics	Animal		X		X	
Sangamo Therapeutics	Therapeutics	X				
Sigma Aldrich	Research	X			X	
ThermoFisher	Research		X	X		
ToolGen	Research			X		
Transposagen	Research			X		
Ziopharm	Therapeutics	X				

CRISPR, cluttered regularly interspaced short palindromic repeats; TALEN, transcription activator-like effector nuclease; ZFN, zinc finger nuclease.

Source: BCC Research

The companies in this industry can be differentiated by several factors, including the industry sectors that participate and the gene-editing technologies they are experts in.

The main industry sectors these companies operate within include life science research agriculture animals and therapeutics.

Roughly one-half of the companies listed in the table participate in the life science research tools market segment. These companies may offer genome-editing tools, as well as a broader range of products addressing the genome-editing workflow. These products and services may include modified cell lines or models, detection and analysis kits and design and delivery tools.

The agriculture industry sector includes a small subset of companies consisting of smaller biotech companies (e.g., Cibus, Caribou Biosciences, Calyxt and Precision BioSciences) and large agricultural companies (e.g., Dow AgroSciences and DuPont). The latter have strategic alliance including licensing deals with the genome-editing specialist companies.

In the animals industry sector, there are at least four companies that have developed early technologies; these include Precision BioSciences (through its alliance with Agrivida), Genus, Recombinetics and Synthetic Genomics/Lung Biotechnology. Genus is working on gene editing of pigs and has a partnership with Caribou Biosciences. Recombinetics is using transcription activator-like effector nuclease (TALEN) and MegaNuclease platforms to edit the genomes of several livestock species. Synthetic Genomics is working with lung biotechnology to modify pig genomes so that they are capable of producing human transplantable organs such as kidneys.

In the therapeutics industry sector, several genome-editing companies are pursuing applications. Key companies in this sector include Cellectis, CRISPR Therapeutics, Editas Medical, Intellia Therapeutics and Sangamo Therapeutics. Therapeutics applications for genome editing face several unique technical challenges, including specificity and reduction of off-target effects. These hurdles, together with regulatory requirements, mean that clinical applications are still at least several years away.

The main genome-editing technologies that these companies are developing and marketing include zinc finger nuclease (ZFN), TALEN, CRISPR/Cas9, MegaNuclease and others.

Most companies specialize in one genome-editing platform, while a few companies operate with two platforms. More than one-half of the companies (16) are using CRISPR/Cas9 platforms, while seven companies use ZFN platforms and five use TALEN platforms. Two companies, Cibus and Precision BioSciences, are using next-generation genome-editing technologies.

SYNTHETIC-BIOLOGY FOUNDRIES INDUSTRY

Companies and institutions in the synthetic-biology foundries industry are shown in the table below.

TABLE 64

SYNTHETIC-BIOLOGY FOUNDRIES INDUSTRY

Company/Research Center	Collaborations
Ginkgo Bioworks	More than 20 customers, including Genomatica and Amyris
MIT/Broad Institute	DARPA, Novartis
SynbiCITE	More than 100 academic and industrial partners
SynCTI	GlaxoSmithKline; Illumina, ThermoFisher Scientific, Singer Instruments, Merck Sharp & Dohme, Agilent Technologies, Becton Dickinson, Cmelia
Zymergen	Arzeda for synthetic-biology technology tools

DARPA, Defense Advanced Research Projects Agency.

Source: BCC Research

Synthetic-biology foundries are factories that use robotic assembly lines to build, test and optimize microbial systems on a large scale. Foundries use software and robotic tools to synthesize the DNA construct, insert it into a microbe and test the output in a high-throughput workflow. Foundries allow for rapid prototyping and testing of multiple variants to find the optimal variant for production.

Both institutions and companies have adopted this model for scaling up synthetic-biology projects.

Ginkgo Bioworks, a spinout from the Massachusetts Institute of Technology, designs a synthetic-biology process to meet a particular customer's end-product demand. Customers work in a range of industries including flavors and fragrances, industrial enzymes, nutritional ingredients, cosmetics, sweeteners and pharmaceuticals. Ginkgo designs the organism and develops the production method for obtaining the end product.

The MIT–Broad foundry works with Novartis on prototyping systems for making molecules produced by bacteria in the human gut. The Defense Advanced Research Projects Agency also works with MIT–Broad as part of a broad-ranging funding to develop new products in human health, agriculture and chemistry.

National University of Singapore's Synthetic Biology for Clinical and Technological Innovation (SynCTI) was founded in 2014. SynCTI performs work in three areas of synthetic biology: chassis and vectors; parts and devices; and testbeds. Foundry work involves high-throughput screening platforms used with synthetic DNA parts libraries and directed evolution. This enables testing and screening for cell factories that have high industrial potential.

SynbiCITE, affiliated with the Imperial College of London, operates a foundry with robotic equipment for designing, constructing and validating large gene constructs. This foundry allows industrial partners to prototype chemicals, drugs or materials.

Zymergen is developing microbial systems for industrial biology by using advanced tools in synthetic biology, automation, machine learning and data architecture. Zymergen formed an alliance with Arzeda in 2016 that enhanced its microbial strain design capabilities.

PHARMACEUTICALS INDUSTRY

The pharmaceutical industry uses a variety of strategies to leverage synthetic biology. The table below shows the various strategies that companies developing synthetic-biology-based drugs are taking.

TABLE 65

PHARMACEUTICALS INDUSTRY SYNTHETIC-BIOLOGY STRATEGIES

Company	Synthetic-Biology Focus	Disease Target Focus	Key Strategies
Abeona Therapeutics	Genome editing	Hematological rare blood diseases	Tool developer
Agilis Biotherapeutics	DNA drugs	Rare genetic diseases	Partner with leading synthetic-biology tools company, Intrexon, to enhance DNA constructs
Ambrx	Nonnatural amino acids	Metabolic diseases	Partner with large drug firms for clinical trials
Baxalta	Genome editing	Cancers	Partnered with Precision BioSciences
Biogen	Gene therapy drugs	Hemoglobinopathies	Partner with Sangamo Therapeutics to use advanced gene-editing tools to develop drugs
bluebird bio	Genome editing	CAR-T therapies	Uses TALEN genome-editing platform and partnered with Celgene and Kite Pharma
Cellectis	Genome editing	Cancers	Developer of TALEN genome-editing technology, partner with Pfizer
Cellgene	Antibiotics; genome editing	Infectious diseases; immuno-oncology	Partner with synthetic biology firms for production platform and genome-editing tools
CRISPR Therapeutics	Genome editing	CAR-T and other therapies	Uses CRISPR/Cas9 platform and partnered with Celgene/GlaxoSmithKline
Demuris	Antibiotic production platform	Infectious diseases	Uses synthetic-biology tools to enhance microbial production of antibiotics
DSM	Antibiotic production platform	Antibacterials	Leverage synthetic-biology tools to cut manufacturing time and costs for existing antibiotics
Editas	Genome editing	Rare diseases	Developer of CRISPR/Cas9 genome-editing tools; partnered with various pharma companies
Enbiotix	Engineered bacteriophage agents	Antibacterials	Uses synthetic-biology tools to engineer existing bacteriophages to give enhanced properties

Evolva	Yeast production platforms	Multiple	Uses synthetic biology to develop better yeast production systems for biologics
Huvepharma	Yeast production platform	Malaria	Acquired synthetic-biology-based process for producing artemisinin
Intella Therapeutics	Genome editing	CAR-T therapies	Uses CRISPR/Cas9 platform and partnered with Caribou Biosciences and Novartis
Intrexon	Synthetic-biology tools	Multiple	Leverage tools with multiple exclusive partnerships within the pharmaceutical industry
Johnson & Johnson	Genome-editing tools	Multiple	Partnership with tools provider Transposagen
Juno Therapeutics	Genome-editing tools		Partnership with Editas Medicine
Merck	Production platform	Diabetes	Develops synthetic biology skills through internal R &D and acquisitions or partnerships for drug production
MorphoSys	Antibody discovery platform	Various diseases	MorphoSys has a broad-based antibody discovery platform that incorporates synthetic-biology tools; the company has leveraged this to develop multiple antibody drug candidates
Pfizer	Drug-discovery and production platforms	Various	Pfizer uses synthetic biology in its drug-discovery platform (from MorphoSys) and in some microbial and mammalian production systems
Prokarium	Oral vaccines	Infectious diseases	Prokarium uses synthetic biology to create novel immune cell-targeting bacteria. These bacteria represent a new class of drugs for in vivo vaccine delivery

Sangamo Therapeutics	Genome-editing tools	Various	Partners with pharmaceutical companies that use its genome-editing tools for drug discovery and production
Seqirus	Vaccine production platform	Influenza	Seqirus leveraged synthetic-biology technology from Synthetic Genomics to create a cell-based vaccine production platform
Shire	Drug discovery	Monogenic diseases	Uses Sangamo Therapeutics's gene-editing technology to discover new drug candidates
Soligenix	Drug discovery	Meliodosis	Uses Intrexon's synthetic-biology tools to discovery new drug candidates
SutroVax	Vaccine production platform	Infectious diseases	Uses Sutro's cell-free production platform to produce vaccines
Synthetic Biologics	Antibody discovery	Infectious diseases	Leverages Intrexon's toolkit to discovery novel antibodies
Transposagen Biopharmaceuticals	Genome editing	CAR-T therapies	Uses CRISPR/Cas9 platform and is partnered with Johnson & Johnson
Vertex Pharmaceuticals	Genome editing	Genetic diseases	Partnership with CRISPR Therapeutics
VG Life Sciences	Cancer drugs	Cancers	Uses its metabolic disruption technology to discover novel cancer drugs
Ziopharm	Drug-discovery platform	Cancers	Uses Intrexon's synthetic-biology tools for cancer drugs targeting immune system pathways

CAR, chimeric antigen receptor; CRISPR, cluttered regularly interspaced short palindromic repeats; GSK, GlaxoSmithKline; R &D, research and development; TALEN, transcription activator-like effector nuclease.

Source: BCC Research

Some companies partner with synthetic-biology tool firms to access drug-discovery or drug-production platforms. These include Agilis Biotherapeutics (Intrexon), Biogen (Sangamo Therapeutics), Cellgene (Sutro), Shire (Sangamo Therapeutics) and Soligenix (Intrexon).

Another group of companies uses their own synthetic biology capability for discovering or producing drugs including Demuris, DSM, Enbiotix and Evolva.

Several synthetic-biology companies have taken a primary strategy of licensing their technology to pharmaceutical firms. These companies include Intrexon, Sangamo Therapeutics and MorphoSys.

Several companies have leveraged synthetic biology to develop new drug classes. These include Enbiotix (engineered bacteriophages) and Prokarium (in vivo targeted vaccines via immune cell-targeting bacteria).

Several of the large pharmaceutical companies are using synthetic biology for drug production platforms, including Merck (Januvia), Seqirus/Novartis (vaccines) and Huvepharma (artemisinin).

Genome editing has come to the forefront of synthetic-biology tools used in pharmaceutical discovery and development. Genome-editing-tool developers have taken the strategy of partnering with larger pharmaceutical companies to bring therapies to market. These alliances include Precision BioSciences (partnered with Baxalta), bluebird bio (Celgene and Kite Pharma), CRISPR Therapeutics (Celgene and GlaxoSmithKline), Transposagen Biopharmaceuticals (Johnson & Johnson), Editas Medicine (June Therapeutics), Intellia Therapeutics/Caribou Biosciences (Novartis) and Intrexon (Ziopharm).

The microbiome therapeutics industry is shown in the table below.

TABLE 66

MICROBIOME THERAPEUTICS INDUSTRY

Company	Indication	Technology Approach
AOBiome	Topical, skin, inflammatory conditions	Ammonia-oxidizing bacteria to restore that part of biome disrupted by modern hygiene practices
Enterome	Inflammatory bowel disease, Crohn’s disease, ulcerative colitis	Analytical tools to measure total fecal bacterial gene content and characterize metagenome; screen metagenomics libraries to discover new drugs and targets
Evelo Biosciences	Cancer, autoimmune and inflammatory diseases	Oral drugs
Kallyope	Diseases that involve the gut and/or gut-brain axis	CNS–gut interactions
Miomics BioTherapeutics	Immune-system-related diseases, including RA, MS, diabetes, IBS, celiac disease, Crohn’s disease and obesity	Oral biologics
Osel Inc.	Women’s health	Live biotherapeutic products (bacterial strains)

Rebiotix	Recurrent *Clostridium difficile* infection.	Microbiota restoration therapy
Second Genome	Crohn's disease	Discovery platform to identify small molecules, bacterial strains or peptide biologics
Seres Therapeutics	*C. difficile* gut infections	Microbiome therapeutics platform and ecobiotic drugs
Synlogic	Rare metabolic disorders	Synthetic biotics
Vedanta Biosciences	Autoimmune and inflammatory diseases	Proprietary consortia of most potent regulatory T-cell inducing *Clostridium* bacteria in human gut
Whole Biome	Metabolic syndrome	Microbiome diagnostic discovery platform

CNS, central nervous system; IBS, irritable bowel syndrome; MS, multiple sclerosis; RA, rheumatoid arthritis.

Source: BCC Research

The microbiome therapeutics industry is an example of a niche market segment where a range of technology approaches are being used, including synthetic biology. Synthetic-biology approaches are being taken by Synlogic and Vedanta Biosciences but there are also other approaches being employed.

Technology approaches in this industry include fecal microbiota transplants (FMTs; ingesting the healthy stool of someone else), defined mixtures, small molecules and engineered bacteria. Synthetic-biology approaches are used for engineered bacteria. Companies using synthetic biology include Vedanta Biosciences and Synlogic.

In addition to these companies, organizations such as Open Biome function to assist the microbiome field. Open Biome is a nonprofit stool bank, providing access to fecal transplants and facilitating research into the human microbiome. The organization works with clinicians to assist in FMT procedures.

AGRICULTURE INDUSTRY

The main competitors in the synthetic-biology agriculture industry are shown in the table below.

TABLE 67

SYNTHETIC-BIOLOGY AGRICULTURE INDUSTRY

Company	Description of Synthetic-Biology Activity
Acadia	Genome editing of crops to replicate genetic variants discovered from high-throughput screening and breeding
BASF	Using genome engineering to develop new crop types
Bayer AG	Licensed CRISPR/Cas9 genome-editing technology from CRISPR Therapeutics and ERS Genomics

Caribou Biosciences	Genome-edited (CRISPR) nonrow crops and major agricultural crops (through its alliance with DuPont)
Cellectis	Genome-edited crops through its Calyxt subsidiary
Cibus	Genome-edited (RTDS oligos) crops
Dow AgroSciences	Genome-edited (ZFN) crops
DuPont Pioneer	Licensed CRISPR/Cas9 genome-editing technology from Caribou Biosciences
ERS Genomics/CRISPR Therapeutics	Genome-edited (CRISPR) crops
Monsanto	Uses ZFN technologies to develop better crop seeds
Precision BioSciences	Genome-edited (MegaNuclease) crops
Recombinetics	Genome editing (TALEN) for livestock, with focus on dairy and beef cattle
Two Blades Foundation	Genome-edited crops, with focus on diseases resistance in Africa

CRISPR, cluttered regularly interspaced short palindromic repeats; oligos, oligonucleotides; RTDS, Rapid Trait Development System; TALEN, transcription activator-like effector nuclease; ZFN, zinc finger nuclease.

Source: BCC Research

The agriculture industry is a growing user of synthetic-biology tools, particularly the field of genome editing for crop improvement. The companies involved include those in the table.

Several of the companies have developed a broad genome-editing capability for multiple market areas, including medicine and agriculture. These companies include Cellectis, Caribou Biosciences, ERS Genomics/CRISPR Therapeutics, Editas, Precision BioSciences and Sangamo Therapeutics. These companies are interested in applying their technologies to a wide range of markets and have either licensed out or formed agricultural-focused subsidiaries to pursue the agriculture market.

A second group of companies have focused on agricultural applications. These include Two Blades Foundation (a nonprofit organization using TALENs), Recombinetics (use of TALENs for livestock), Cibus (focus on insecticide- and pest-resistant crops) and Acadia.

The large companies in the agricultural biotechnology industry include Bayer, DuPont Pioneer, Groupe Limagrain, Monsanto, Syngenta, Dow, JR Simplot, BASF and Taloo. Many of these larger companies are active in synthetic-biology agriculture development.

Bayer has alliances with two genome-editing companies, CRISPR Therapeutics and ERS Genomics. These relationships position Bayer in synthetic-biology tools for agriculture and other industries

BASF uses synthetic biology extensively for industrial biotechnology applications. For agriculture, the company is working through its SunGene GmbH subsidiary, to develop new ways for precisely engineering plant genomes.

Dow AgroSciences is a large agricultural company that has successfully used genome-editing technology to introduce multiple traits into food crops, using Sangamo Therapeutics's ZFN genome-editing tools.

DuPont likewise has an alliance with Caribou Biosciences for CRISPR/Cas9 development. DuPont is developing a corn product that has been modified with CRISPR/Cas9 tools.

Monsanto is using Sangamo Therapeutics's zinc finger protein technology, called SmartStax. These seeds increase crop yields, reduce production costs and have higher resistance to pathogens.

ACQUISITIONS AND STRATEGIC ALLIANCES

The table below shows key acquisitions in the synthetic-biology industry for 2014 through 2016.

TABLE 68

SYNTHETIC-BIOLOGY INDUSTRY ACQUISITIONS, 2014-2016

Acquiring Company	Target Company	Year	Strategic Objective
Cargill Inc.	OPX Biotechnologies	2015	Gave Cargill synthetic biology capability for expanding its market beyond traditional markets in food and feed
Dow Chemical	DuPont	2016	Brings together synthetic biology expertise in agriculture, materials science and industrial chemicals applications
DuPont	Dyadic	2015	DuPont acquired the industrial enzymes assets of Dyadic
Evolva	Allylix	2014	The acquisition exploited high synergies in the companies' yeast fermentation platforms
Huvepharma	Sanofi-Aventis (semisynthetic artemisinin business)	2016	Huvepharma vertically integrated into the semisynthetic artemisinin production chain with this acquisition
Integrated DNA Technologies	AITbiotech Pte	2015	Acquires oligonucleotide synthesis business in Southeast Asia region
Integrated DNA Technologies	MBiotech	2016	Gains a sales and distribution network in the South Korea market
Joule Unlimited	Red Rock Biofuels	2016	Joule acquires a biofuels supply outlet
Novartis	GlaxoSmithKline oncology business	2014	This strengthened Novartis' position in the oncology drugs business, a key focus for genome-editing technologies
Renewable Energy Group	LS9	2014	Acquisition provides a strong commercial partner for LS9's synthetic-biology platforms

Thermo Fisher Scientific	Life Technologies Inc.	2014	Brings a set of synthetic-biology tools into the Thermo Fisher Scientific sales and distribution network
Twist Bioscience	Genome Compiler Corp.	2016	Positioned Twist to participate in the e-commerce-based synthetic DNA business

Source: BCC Research

Key acquisitions during this period include Thermo Fisher Scientific's acquisition of Life Technologies Inc. and the merger of DuPont and Dow Chemical. Life Technologies brought considerable synthetic-biology tools to Thermo Fisher, including in genome editing, DNA synthesis and sequencing, and cell culture media. This was an important acquisition for the synthetic-biology research tools industry.

The Dow/DuPont merger is important for synthetic biology because each company is active in synthetic biology and has access to important end markets. These markets include industrial and specialty chemicals and agriculture.

A brief synopsis of each acquisition during this period is given below.

Cargill, Inc. acquired OPX Biotechnologies in April 2015. OPX is developing synthetic-biology methods with applications in biorefining and biofuels. The acquisition strengthened Cargill's fermentation business beyond its traditional markets in food and feed.

In July 2016, the stockholders of Dow Chemical and DuPont voted to approve a merger between the two companies. Both companies are active in synthetic biology, and the merger should strengthen the overall synthetic-biology toolbox of the two companies. Applications include agriculture, materials science and industrial chemicals.

In December 2015, DuPont acquired the C1 industrial enzyme assets of Dyadic. Together with DuPont's 2011 acquisition of Danisco, this strengthened DuPont's industrial enzyme business.

In November 2014, Evolva acquired Allylix, gaining access to a platform for producing high value ingredients for the flavors, fragrances and cosmetics industries. Allylix products are highly complementary to Evolva's yeast-based production methods, and this acquisition strengthened Evolva's yeast fermentation business.

Huvepharma purchased the synthetic-biology-based semisynthetic artemisinin plant from Sanofi in 2016. This acquisition allowed Huvepharma to control the full value chain for semisynthetic artemisinin.

International DNA Technologies (IDT) made two acquisitions in 2015/2016 that strengthened its global DNA-synthesis business. In December 2015, IDT acquired the oligonucleotide synthesis business of AITbiotech Pte Ltd. (Singapore), allowing for expansion into Southeast Asia.

In June 2016, IDT acquired the South Korean company, MBiotech Inc., providing distribution and marketing strength in the South Korea market.

In January 2016, Joule Unlimited acquired Red Rock Biofuels. Red Rock is contracted with FedEx to supply three million gallons of biofuel per year through 2024, using wood waste as a fuel source. This acquisition positions Joule, a biofuels-oriented synthetic-biology company, in the alternative jet-fuel industry.

In 2014, Novartis acquired the oncology business of GlaxoSmithKline, significantly strengthening its global position in oncology drugs. This is relevant to synthetic biology because a key focus of genome-editing technologies is in the field of immuno-oncology.

Renewable Energy Group (REG) acquired LS9 in January 2014. The acquisition allows REG to expand its biodiesel business into value-added chemicals using LS9's synthetic-biology platforms. REG has extensive experience in scale-up of chemical processes, and this should help to accelerate commercialization of LS9's products.

Thermo Fisher Scientific completed a strategic acquisition of Life Technologies Inc. in February 2014. This acquisition strengthens Thermo Fisher's life science research tools business. It also adds significant synthetic-biology tools to Thermo Fisher's product portfolio. These tools include genome editing, gene synthesis, DNA sequencing, cell culture media and bioinformatics.

In April 2016, Twist Bioscience acquired Genome Compiler Corp. (Israel). Genome Compiler's technology is in e-commerce and digital products, and this acquisition gives Twist the ability to integrate its DNA-synthesis business with an e-commerce platform.

The synthetic-biology industry was very active in structuring partnerships and alliances from 2014 through 2016. The table below shows important strategic alliances in the synthetic-biology industry during this period.

TABLE 69

STRATEGIC ALLIANCES, 2014-2016

Company	Alliance Partner	Year	Strategic Objective
Agrivida	Precision BioSciences	2014	Use genome editing to produce desirable traits for agriculture applications
Amyris	Dowel C &I Co. Ltd.	2014	Distribution of the specialty chemical, squalane, in South Korea
GlaxoSmithKline	Codexis	2014	Transfer of synthetic-biology tools for developing pharmaceutical production enzymes
Global Bioenergies	Audi	2014	Joint development of renewable isooctane for gasoline engines
Rennovia	Johnson Matthey	2014	Development of catalysts for producing glucaric acid and ADA
Sangamo Therapeutics	Biogen	2014	Develop therapies for hemoglobinopathies
Sutro Biopharma	Johnson & Johnson	2014	Formed new company, SutroVax, to develop new vaccines using Sutro's platform technology

AstraZeneca	Wellcome Trust, Broad Institute, Innovative Genomics Initiative, Thermo Fisher Scientific	2015	Provided access to genome-editing tools for drug development and discovery programs
BASF	Genomatica	2015	Extended earlier agreement to cover production of synthetic-biology-enabled BDO in Southeast Asia region
Bayer	CRISPR Therapeutics	2015	Alliance to discover new therapeutics as well as agricultural uses for genome-editing tools
Caribou Biosciences	DuPont	2015	Extended genome-editing technology into various multiple markets
Caribou Biosciences	Novartis	2015	Extended genome-editing technology into drug development market
Codexis	Merck & Co.	2015	Merck gained access to synthetic-biology-based enzyme tools, strengthening its drug-production capabilities
Editas Medicine	Juno Therapeutics	2015	Extended Editas' genome-editing platform to cancer therapies
Intrexon	Dominion Resources	2015	Intrexon partners with a feedstock source for converting natural gas to isobutanol
LanzaTech	ArcelorMittal/Primetals Technologies	2015	Alliance to build a commercial plant producing ethanol from waste gas deriving from steel-making operations
Merck & Co	Codexis	2015	Merck obtained license to CodeEvolver for optimizing enzymes used in biomanufacturing
Merck & Co	Synthace	2015	Combines Merck's biomanufacturing with Synthace's biologic programming expertise
Novartis	Caribous Biosciences	2015	Novartis accesses genome-editing tools for drug research purposes
Novartis	Intellia Therapeutics	2015	Novartis accesses genome-editing technologies for therapy development
Precision BioSciences	Baxalta Inc.	2015	Joint development of CAR-T therapies using genome-editing technologies
Radiant Genomics	Dow AgroSciences	2015	Use of synthetic biology in crop protection applications
Sigma Aldrich	Genewiz/Oxford Genetics	2015	Streamlines gene ordering process for research scientists
Synthace	Dow AgroSciences	2015	Extended the application for Synthace's synthetic-biology software platform to the agriculture field
Synthetic Genomics	Lung Biotechnology	2015	Extended an earlier agreement covering genome modifications to pig genomes
Synthetic Genomics	Gen9	2015	Transfer of key tools to Gen9 for its DNA-synthesis businesses

Amyris	Givaudan	2016	Extends Amyris' market applications to fragrance ingredients
Arzeda	Gen9	2016	Secures a source of synthetic DNA for developing cellular factories
Bayer	ERS Genomics	2016	Provided Bayer with access to genome-editing technology, broadening its IP position
Bolt Threads	Patagonia	2016	Adds a strong end marketing partner for Bolt Thread's synthetic-biology-enabled fabrics
Calysta Inc.	Chain Biotech/ University of Nottingham	2016	Develop synthetic-biology-enabled microbial systems to transform methane gas into nutritional products
Caribou Biosciences	Genus PLC	2016	Extended genome-editing technology into livestock market
Caribou Biosciences	Integrated DNA Technologies	2016	Extended genome-editing technology into life science research market
Cell Design Labs	Kite Pharma	2016	Alliance gave Kite access to innovative synthetic-biology tools for drug development
Demuris	Dundee Cell Products	2016	Agreement covers use of synthetic-biology tools to expand Demuris' antibiotic pipeline
Dow AgroSciences	Radiant Genomics	2016	Use of synthetic-biology tools for natural-product discovery and development
Dow AgroSciences	TeselaGen	2016	Software for designing and editing DNA
Eurofins	Agilent Technologies	2016	Eurofins gained access to cloning tools as a complement to its gene- synthesis services
Gevo	Musket Corp.	2016	Enhances distribution for Gevo's isobutanol in Western U.S.
Ginkgo	Amyris	2016	Combines synthetic-biology platforms for producing products in a range of industries
Global Bioenergies	IBN-One/Lantamannen Aspen	2016	Expanded renewable isooctane to specialty fuel applications
Green Biologics	Acme-Hardesty	2016	Secured distribution outlet for renewable specialty chemicals
Green Biologics	Nexeo Solutions	2016	Obtained distribution outlet for renewable n-butanol and acetone in the U.S.
Intellia Therapeutics	Regeneron Pharmaceuticals	2016	Regeneron gained access to genome-editing technology for its in vivo therapeutics programs
LanzaTech	Aemetis Inc.	2016	Aemetis obtained exclusive license to LanzaTech synthetic-biology technology for producing ethanol

LanzaTech	Global Bioenergies	2016	Global Bioenergies obtained exclusive license to LanzaTech synthetic-biology technology for producing isobutene
Metabolix	Tepha Inc.	2016	Tepha gained access to Metabolix's biopolymer platform for medical applications
Rennovia	Stora Enso	2016	Use of synthetic-biology-based catalysts for producing novel chemicals
SGI-DNA	VWR	2016	Enables wider distribution of synthetic-biology reagents in North America and Europe
Synlogic	AbbVie	2016	Covers use of Synogic's synthetic-biology platform to develop treatments for inflammatory bowel diseases
Synthace	Microsoft	2016	Added a cloud delivery platform to Synthace's synthetic-biology software package
Synthetic Genomics	VWR	2016	Extended the distribution of important synthetic-biology tools such as Gibson Assembly kits
Twist Bioscience	Desktop Genetics	2016	Twist extends its DNA-synthesis workflow capabilities with this alliance
Zymergen	Arzeda	2016	Zymergen accesses synthetic-biology design tools to complements its microbial strain platform

ADA, adipic acid; BDO, 1,4-butanediol; CAR, chimeric antigen receptor; IP, intellectual property.

Source: BCC Research

The data in this table illustrate several key trends within the synthetic-biology industry.

Several industries stand out in their high interest in synthetic biology, and this is reflected in the number of alliances during this period. These industries include pharmaceuticals, agriculture, research tools and industrial biotechnology.

Many alliances by synthetic-biology companies were focused on capturing a larger share of the workflow value chain. Examples of this activity included Intrexon/Dominion Resources (extended value chain into feedstock sources), Merck & Co/ Synthace and Codexis (extended value chain into enzyme optimization and software), Eurofine and Agilent Technologies (extended gene-synthesis value chain into cloning) and Twist Bioscience and Desktop Genetics (extended genome-editing value chain into design and guide libraries).

Several companies formed alliances with software/cloud companies to enhance their synthetic-biology offerings, including Sigma Aldrich/Genewiz/Oxford Genetics, Dow AgroSciences/TeselaGen and Synthace/Microsoft.

Genome-editing companies were very active in forming alliances with established end-user partners, thus strengthening the development of applications for their

technologies. Examples of this include Editas Medicine (June Therapeutics), Precision BioSciences (Baxalta), ERS Genomics (Bayer), Caribou Biosciences (Genus, Integrated DNA Technologies) and Intellia Therapeutics (Regeneron Pharmaceuticals).

A brief synopsis of each of the industry alliances during 2014 through 2016 is provided below.

In March 2014 Agrivida formed an alliance with Precision BioSciences covering developed of desirable traits for agricultural applications.

In February 2014, Amyris formed a partnership with Dowell C&I Co. Ltd. covering the distribution of Amyris' Neossance Squalane product in South Korea.

In July 2014, GlaxoSmithKline formed a partnership with Codexis. Under this agreement Codexis has transferred its CodeEvolver platform for developing production enzymes to GlaxoSmithKline. The parties announced in May 2016 that this transfer had been successfully completed, thus strengthening GlaxoSmithKline's ability to manufacture small-molecule pharmaceuticals.

In January 2014, Global Bioenergies formed an alliance with Audi (Germany) to develop renewable isobutene-derived isooctane for use in gasoline engines. This alliance demonstrated the high interest in the use of renewable isobutene on the part of a major automobile manufacturer.

In March 2014, Rennovia formed an alliance with Johnson Matthey to use advanced biocatalysts for producing glucaric and adipic acids from glucose. This provides a commercial outlet for Rennovia's biocatalyst technologies

In January 2014, Sangamo Therapeutics entered into a strategic alliance with Biogen covering the development of therapeutics for hemoglobinopathies. Biogen will use Sangamo Therapeutics's gene-editing technologies to development therapies for sickle cell disease and beta-thalassemia.

In January 2014, Sutro and Johnson & Johnson cofounded a new company, SutroVax. SutroVax will use Sutro Biopharma's Xpress CF cell-free protein synthesis platform to develop new vaccines for a range of diseases.

In January 2015, AstraZeneca entered four research collaborations covering the use of CRISPR technology for its drug-discovery and development programs. The four institutions involved were the Wellcome Trust Sanger Institute, the Innovative Genomics Initiative, Thermo Fisher Scientific and the Broad Institute. These alliances provided AstraZeneca with genome-editing know-how for its drug development efforts, particularly in immuno-oncology.

In September 2015, BASF extended an earlier agreement with Genomatica, which uses a modified *E. coli* fermentation process for its butane diol (1,4-butanediol; BDO) process. The fermentation process uses dextrose as a renewable feedstock. This extension gave BASF the rights to build a plant in Southeast Asia, which would use Genomatica's Geno BDO process technology.

Bayer formed two alliances in genome editing during 2015/2016. The alliances are with CRISPR Therapeutis and ERS Genomics, and significantly broadened Bayer's ability to use genome-editing tools for industrial and medical applications.

Caribou Biosciences, a genome-editing company, formed several partnerships in 2015 and 2016. These alliances extended Caribou's development programs into new markets including livestock (Genus PLC in May 2016), life science research (Integrated DNA Technologies in February 2016), multiple markets (DuPont in October 2015) and drug development tools (Novartis in 2015).

Codexis formed an alliance with Merck & Co in August 2015. The alliance gave Merck access to Codexis' synthetic-biology-based enzyme tools for developing biocatalysts for its diabetes and hepatitis C products. This strengthened Merck's production capabilities for these drug classes.

In May 2015, Editas Medicine partnered with Juno Therapeutics, in which the companies began a joint development effort in chimeric antigen receptor (CAR)-T and high-affinity T-cell receptor cancer therapies. This alliance extended the applications for Editas' genome-editing technologies into the cancer therapy field.

In August 2015, Intrexon formed a partnership with Dominion Resources to develop and scale-up a process for converting natural gas to isobutanol. Dominion Resources owns large natural gas reserves that could be used as the feedstock. In March 2016, Intrexon announced that the pilot plant for this process became operational.

In July 2015, LanzaTech announced a collaboration with ArcelorMittal (a leading steel and mining company) and Primetals Technologies (a technology and service provider to the iron and steel industry). The companies agreed to build a commercial-scale production plant for producing 47,000 tons per year of bioethanol from waste gases generated from steel-making operations.

In November 2015, Synthace and Merck & Co. formed an alliance to develop advanced biomanufacturing technologies. Based on their agreement, Merck will have access to Synthace's Antha biologic programming software, which can aid Merck in its biomanufacturing activities.

In August 2015, Merck reached a licensing agreement with Codexis covering the use of CodeEvolver enzyme tools for use in pharmaceutical production processes. This strengthened Merck's synthetic-biology capabilities in this area.

In January 2015, Novartis formed two partnerships in the genome-editing field, with Intellia Therapeutics and Caribou Biosciences. The Intellia deal was for CRISPR/Cas9 technologies for use in developing therapeutics for blood disorders. The Caribou Biosciences deal was for CRISPR/Cas9 technologies for use in drug research. These alliances gave Novartis access to key technologies in the genome-editing field.

Baxalta Inc. formed a partnership with the genome-editing firm, Precision BioSciences, in February 2015. The companies will jointly develop CAR-T-cell therapies using Precision's genome-editing platform for cancer applications. This collaboration gives Baxalta entry into the genome-editing field for drug development.

In February 2015, Radiant Genomics partnered with Dow AgroSciences. Dow gained rights to use Radiant's synthetic-biology-based natural products in its crop protection programs.

Sigma Aldrich's November 2015 alliance with Genewiz and Oxford Genetics is aimed at streamlining the process of ordering synthetic genes for the life science research community. The alliance makes available to researchers the ability to order a gene together with the relevant vector through the internet.

In October 2015, Synthace reached an agreement with Dow AgroSciences to extend Synthace's Antha synthetic-biology software platform to applications in the agricultural field.

In September 2015, Synthetic Genomics extended an earlier collaboration with Lung Biotechnology covering the development of transplantation-ready pig organs using SGI platforms. This agreement is aimed at redesigning pig genomes to create pigs that will grow human-transplantable organs such as kidneys.

In June 2015, Synthetic Genomics licensed a range of DNA-synthesis-related technologies to Gen9 Inc. This partnership strengthened Gen9's capabilities in the gene-synthesis business by giving it access to microarray-based high-throughput DNA tools.

In June 2016, Amyris formed a collaboration with Givaudan covering the development and commercialization of proprietary fragrance ingredients using Amyris' Hi-Ryse platform.

In April 2016, Arzeda formed a partnership with Gen9 covering the supply of large quantities of synthetic DNA that Arzeda will use in its development programs. This alliance secures DNA material for Arzeda to develop cell factories for industrial applications.

In May 2016, Bolt Threads, developing synthetic-biology-enabled fabrics, formed a partnership with Patagonia. Patagonia is a leading outdoor clothing company, and this alliance significantly strengthened Bolt Thread's ability to commercialize its textile products.

In May 2016, Calysta Inc. formed an alliance with the University of Nottingham and Chain Biotech to use synthetic biology to develop microbial platforms that can ferment methane gas into omega 3 nutritional products.

Cell Design Labs formed an alliance with Kite Pharma in June 2016, giving Kite access to Cell Design's innovative on–off switches for developing treatments for acute myeloid leukemia, as well as for other CAR-T-cell therapies. This partnership strengthened Kite Pharma's synthetic-biology technology portfolio for its drug pipeline.

In April 2016, Demuris formed an alliance with Dundee Cell Products. This agreement covered the use of synthetic-biology methods for discovering antibiotics within existing libraries. This agreement will help to expand the range of antibiotics in Demuris' pipeline.

Dow AgroSciences formed two alliances during 2016 that strengthened its position in synthetic biology. The first was with Radiant Genomics (February 2016) covering natural/product discovery and development. The second was with TeselaGen Biotechnology (April 2016), which extended Dow's synthetic-biology workflow by using software for designing and editing DNA.

In March 2016, Eurofins and Agilent Technologies formed an alliance, giving Eurofins access to Agilent's cloning kits. These cloning kits complement Eurofin's gene-synthesis service business.

In June 2016, Gevo formed an agreement with Musket Corp., which gives Gevo distribution capabilities for its isobutanol products for marine and off-road gasoline in the Western U.S.

In June 2016, Ginkgo formed an alliance with Amyris; this is a broad-ranging partnership for development and scale-up of synthetic-biology-based products in the cosmetics, jet fuel and industrial lubricants industries.

In July 2016, Global Bioenergies partnered with IBN-One and Lantamannen Aspen. Aspen, a leader in two and four-stroke engines, obtained rights to renewable isooctane for its specialty fuel applications. This alliance helped to expand the market range of a synthetic-biology-derived fuel to specialty engine applications.

In March 2016, Green Biologics formed an alliance with Acme-Hardesty. Acme-Hardesty will market Green Biologics' synthetic-biology-derived n-butanol an acetone to several industries, including food ingredients, cleaning products and biolubricants.

In April 2016, Green Biologics formed a partnership with Nexeo Solutions; the alliance covered the distribution of n-butanol and acetone to various specialty chemicals industries in the U.S.

In April 2016, Intellia Therapeutics partnered with Regeneron Pharmaceuticals, giving Regeneron the rights to genome-editing technology for discovery and development of pharmaceuticals.

In March 2016, LanzaTech exclusively licensed Aemetis Inc. its technology for converting waste matter (agricultural, forest, dairy and construction wastes) to ethanol. Aemetis' existing 60 million gallon per year ethanol plant in California will use these new feedstocks to reduce the cost of producing ethanol.

In January 2016, LanzaTech formed an agreement with Global Bioenergies enabling Global Bioenergies to diversify its feedstocks in its isobutene production plant.

In May 2016, Metabolix gave Tepha a license to use its biopolymer synthetic-biology-based platform for medical applications.

In May 2016, Rennovia formed a partnership with Stora Enso, in which Stora Enso will develop synthetic-biology-enabled production processes for several specialty chemicals in the paper, board and tissue industries.

In July 2016, SGI-DNA formed a distribution agreement with VWR covering North America and Europe. VWR will market SGI's synthetic-biology research products, including Gibson Assembly kits and other DNA construct kits, to the life science laboratory industry in these regions.

In February 2016, Synlogic, a developer of synthetic biotics, formed an alliance with AbbVie. The companies will use Synlogic's synthetic-biology platform to develop therapies for inflammatory bowel diseases.

Synthace strengthened its synthetic-biology software platform with an alliance with Microsoft in April 2016. The alliance allowed Synthace to deliver its biologic production systems optimization software program, Antha, on Microsoft's Azure Cloud service.

In July 2016, Synthetic Genomics formed an alliance with VWR, a leading distributor of products and services to laboratories and production plants. This agreement enhances SGI's marketing of synthetic-biology reagents, including the Gibson Assembly DNA cloning suite of products.

In June 2016, Twist formed a partnership with Desktop Genetics in which Desktop's single-guide RNA CRISPR design library services are combined with Twist's guide libraries. The two platforms complement each other and provide a more integrated workflow to synthetic-biology researchers.

In March 2016, Zymergen formed an alliance with Arzeda that provided Zymergen with access to design tool software to aid in its microbial strain engineering activities.

Chapter 7

SYNTHETIC-BIOLOGY MARKETS

SYNTHETIC BIOLOGY: GLOBAL MARKETS

BIO066D
January 2017

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ISBN: 1-62296-433-0

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CHAPTER 7
SYNTHETIC-BIOLOGY MARKETS

INDUSTRY GROWTH-DRIVING FORCES

The key trends driving market growth in synthetic biology are shown in the table below.

TABLE 70

SYNTHETIC-BIOLOGY GROWTH-DRIVING FORCES

Driving Force	Impact on Synthetic-Biology Markets
Emergence of new tools and technologies	Provide a “technology push” for a range of synthetic-biology markets ranging from research to applied markets
Commercialization pathways are speeding up	Non-GMO for genome-edited seeds; development workflow for novel genes for production systems (design, synthesize, verify code, test)
Government support for renewable fuels	Mandates in many countries provide incentives for technical innovation and commercial risk-taking in use of renewable feedstocks
Adoption of new genome-editing technologies	Spans a range of synthetic-biology industries, including research, pharmaceuticals and agriculture/animals
Growth in synthetic-biology foundries	Provides access to end-user community for developing new production pathways for key products

GMO, genetically modified organism.

Source: BCC Research

Growth in the synthetic-biology industry is being driven by a number of factors ranging from emerging technologies to favorable regulations to market needs.

Technology driving forces include the development of new tools in the fields of genome editing, synthetic cells, and next-generation DNA synthesis.

New genome-editing tools, including cluttered regularly interspaced short palindromic repeats (CRISPR)/Cas9 and transcription activator-like effector nuclease (TALEN) systems, are providing researchers with the know-how to make precise, rapid changes to DNA.

Next-generation DNA-synthesis methods are revolutionizing the way DNA is made. These methods use high-density chips or microarrays to make individual oligonucleotides and subsequently assemble these oligonucleotides into longer DNA constructs.

The next-generation DNA-synthesis platforms are leading to gene-synthesis cost reduction and enabling large-scale projects such as Write-DNA and whole-genome synthesis.

Genome editing combined with advanced DNA synthesis greatly accelerates the development cycle for downstream synthetic biology systems and products. For example,

the design, building and testing of new microbial production systems can be aided greatly by the new genome-editing and DNA-synthesis tools.

Minimal synthetic cells are engineered cell lines with genomes that are smaller than those of cells found in nature. Minimal synthetic cells give synthetic biologists the ability to design and build synthetic organisms from the bottom up with predictable results. These systems hold the promise of replacing engineered organisms in next-generation production factories for making pharmaceuticals, biofuels, chemicals and other products.

The speeding up of commercialization pathways is a key driving force for synthetic-biology markets. Examples of this driving force are discussed below for the agricultural and pharmaceutical industries.

In the agriculture market, genome editing has changed the way genetically modified crops are regulated, allowing for faster market introduction. Two important countries in the agriculture sector, the U.S. and Argentina, are moving to not regulate genome editing. This is because genome-edited crops are not distinguishable from those of conventional breeding and they are not produced using a plant pest. The first genome-edited crop to be commercialized, Cibus' SU Canola, is not considered as a GMO (genetically modified organism) by the U.S. Department of Agriculture and thus was approved without costly and long regulatory deliberation.

In the research and pharmaceutical markets, next-generation gene-synthesis technologies are helping to speed up the workflow. When a researcher wants to evaluate a new DNA sequence for a gene, the workflow involves sequence design and synthesis of the new gene, followed by quality analysis to ensure that new sequence matches the design sequence. The process of making the gene is time consuming and complicated. This bottleneck can be addressed by the next-generation synthesis technologies, which can provide faster turnaround and an accurate synthesis product to the researcher.

For some important end markets for synthetic biology, particularly biofuels, local-government mandates are helping to support growth. More than 60 countries have blending mandates for renewable fuels. These mandates are important drivers for synthetic-biology-based processes for producing biofuels such as ethanol or diesel.

For example, the U.S. has significantly increased the mandated volume requirements for biofuels since 2014. The 2016 standard for cellulosic biofuel is 200 million gallons, seven times more than the market produced in 2014. The total renewable biofuel standard for 2016 is 1.8 billion gallons, an 11% increase over the 2014 actual volumes.

The growing popularity of novel genome-editing tools is helping to drive the synthetic-biology markets. The rise of CRISPR/Cas9 and TALEN systems, as well as continuing use of zinc finger nucleases (ZFNs) is responsible for this. Genome editing covers a range of industries, including the research, agriculture and animals, and pharmaceuticals.

The genome-editing industry has experience rapid growth during the past few years, mostly due to the CRISPR platforms. As a tool in synthetic biology, genome editing creates demand for associated enabling and core technologies. For example, the creation of a novel gene sequence requires synthesis of the new gene and subsequent DNA sequence

verification of the base pair order. This increases demand for synthetic genes and enabling technologies for sequencing and design informatics.

Synthetic-biology foundries provide rapid prototyping and testing of microbial variants to achieve optimal production routes. These production routes can then be applied by the end-user customer to produce high-value end products in the chemicals, pharmaceutical and energy industries. This trend helps the growth in the industry by making available to downstream users the design, build and production skills of synthetic biology experts.

Ginkgo Bioworks and Zymergen are two examples of this trend. Both companies use synthetic-biology tools to create integrated production systems for leading end-user companies.

SYNTHETIC-BIOLOGY MARKETS BY END-USER INDUSTRY

RESEARCH MARKET

The synthetic-biology research market, by product type, is shown in the table below.

TABLE 71

GLOBAL VALUE OF RESEARCH MARKET, BY PRODUCT TYPE, THROUGH 2021 ($ MILLIONS)

Product Type	2015	2016	2021	CAGR% 2016–2021
Enabling products	152.3	172.9	287.2	10.7
Biologic components	55.0	62.2	113.1	12.7
Integrated systems	12.0	13.9	83.8	43.2
Enabled products	–	–	–	–
Total	219.3	249.0	484.1	14.2

Source: BCC Research

The research market consists of academic, nonprofit and government life science laboratories.

The global value of the research market in 2016 is $249.0 million, and it is forecast to grow at a 14.2% compound annual growth rate (CAGR), to reach $484.1 million by 2021.

Enabling products and biologic components made up the bulk of this market in 2016. Enabling products include DNA synthesis and assembly, genome editing, informatics, DNA sequencing and specialty media.

Biologic components include synthetic genes, delivery plasmids and BioBrick parts. These technologies and products are used extensively by laboratories for their synthetic-biology-based research programs.

For research laboratories, enabling products such as synthetic genes, DNA sequencing and informatics are critical to performing genome-editing research.

Biologic components are needed by laboratories that are performing synthetic biology experiments in directed evolution, metabolic engineering and heterologous protein expression, among others. The demand for biologic components will continue to increase as the ongoing genomics revolution continues to identify novel genes and their functions. Ready access to synthetic genes, BioBrick parts and delivery plasmids accelerates the industrial scale use of these parts. The ready availability of these tools permits rapid construction of useful DNA constructs, high-throughput testing and redesign of microbes to identify the best producers for a given end product. This permits engineers to more easily incorporate synthetic biology into their pipelines for industrial end products.

The integrated systems market has a high CAGR of 43.2%. Integrated systems include chassis organisms, production systems, and synthetic cells. The bulk of this market consists of *Escherichia coli* minimal genomes and yeast cell factories. Sales for these applications will continue to grow in the future, as well as the use by research and development (R&D) customers of synthetic cells. The synthetic cells market is a newly emerging product category that is projected to have great utility as a tool for fundamental research projects during the coming years.

PHARMACEUTICALS MARKET

The table below gives the market value for synthetic-biology-related products in the pharmaceuticals industry.

TABLE 72

GLOBAL VALUE OF PHARMACEUTIALS MARKET, BY PRODUCT TYPE, THROUGH 2021
($ MILLIONS)

Product Type	2015	2016	2021	CAGR% 2016–2021
Enabled products	1,253.5	1,326.1	3,838.5	23.7
Enabling products	443.1	503.1	957.2	13.7
Biologic components	119.8	140.5	285.1	15.2
Integrated systems	27.2	34.3	278.1	52.0
Total	1,843.6	2,004.0	5,358.9	21.7

Source: BCC Research

Synthetic biology is important in pharmaceuticals by allowing companies to develop fully the opportunity space for a given protein. This is possible since the coding sequence for any particular protein can be mutated randomly and optimized using rapid DNA-synthesis

formats. Besides use in drug-discovery and proteomics applications, synthetic-biology tools can be used for developing more efficient production systems for drugs, particularly antibiotics and vaccines.

The synthetic-biology market in the pharmaceutical industry was valued at $2.0 billion in 2016, and it is growing at a rate of 21.7% to reach a forecast value of nearly $5.4 billion by 2021.

A significant portion of these products are enabled products, that is, drugs for infectious diseases, diabetes, malaria and vaccines. The enabled products market was just over $1.3 billion in 2016 and is growing at a CAGR of 23.7% to reach over $3.8 billion by 2021.

Growth in enabled drug products is driven by the demand for drugs for key infectious diseases and diabetes being produced by synthetic-biology methods. These products include cephalosporins, vaccines, stigplatin and artemisinin.

Enabling products were also a significant portion of the pharmaceutical industry, with a market value of $503.1 million in 2016. This market segment is growing at a CAGR of 13.7% to reach a forecast value of $957.2 million by 2021.

Enabling products' growth is being driven by the use of new genome-editing tools for drug discovery and development, as well as strong demand for DNA sequencing to verify the fidelity of edited DNA constructs.

The biologic components market segment was valued at $140.5 million in 2016, and is forecast to grow at a CAGR of 15.2% to reach $285.1 million by 2021. Biotechnology and pharmaceutical companies are important consumers of synthetic genes, accounting for up to one-half of all synthetic genes produced by the industry. This demand is being driven by the popularity of genome-editing methods for drug discovery and development.

The integrated systems market segment, including chassis organisms and production systems, was valued at $34.3 million in 2016 and is growing at a CAGR of 52.0% to reach $278.1 million by 2021. The demand for integrated systems is being driven by the need for more efficient production of drug compounds.

CHEMICALS MARKET

The table below shows the global value of the synthetic-biology chemicals market, by product type.

TABLE 73

GLOBAL VALUE OF CHEMICALS MARKET, BY PRODUCT TYPE, THROUGH 2021 ($ MILLIONS)

Product Type	2015	2016	2021	CAGR% 2016–2021
Enabled products	1,147.7	1,250.3	3,329.9	21.6
Enabling products	62.3	70.7	277.6	31.5
Integrated systems	23.0	30.0	219.3	48.9
Biologic components	7.6	8.8	29.0	26.9
Total	1,240.6	1,359.8	3,855.8	23.2

Source: BCC Research

The market for synthetic-biology products in the chemicals industry was over $1.3 billion in 2016 and is growing at a CAGR of 23.2%, to reach a forecast size of over $3.8 billion by 2021.

The chemicals market is dominated by enabled products, with sales of over $1.1 billion in 2016 and growing to a market size of over $3.3 billion by 2021. Enabled products consist of enzymes, cosmetics, flavors and fragrances, lubricants, polymers and surfactants.

There is much interest in the chemical industry to look at alternatives to fossil fuels to produce chemical products. The motives for this include reducing the carbon footprint, being more environmentally friendly and reducing dependence on oil as a raw material. Synthetic biology provides a viable alternative production platform for making chemicals and avoiding the use of oil-derived starting materials.

The chemicals industry is very diverse, with many sectors and specific requirements and needs. There is a need for products that are designed to meet various end-user requirements, and synthetic-biology tools have emerged as effective methods to achieve this. Synthetic biology allows for producers to achieve a better-performing specialty chemical (e.g., Evolva’s new EverSweet stevia product; or Spiber’s ultrastrong high-performance outerwear fiber) or a more sustainable production process (e.g., DuPont’s bio-PDO [1,3-propanediol] for Sorona fiber).

These performance advantages imparted to the product by synthetic-biology-based production processes are helping to drive growth in the market segments within the chemicals industry.

ENERGY MARKET

The table below shows the global value of the energy market, by product type.

TABLE 74

GLOBAL VALUE OF ENERGY MARKET, BY PRODUCT TYPE, THROUGH 2021
($ MILLIONS)

Product Type	2015	2016	2021	CAGR% 2016–2021
Enabled products	186.4	216.6	589.9	22.2
Enabling products	20.8	23.6	76.6	26.6
Biologic components	3.9	4.5	9.3	15.6
Integrated systems	3.7	5.2	38.5	49.2
Total	214.8	249.9	714.3	23.4

Source: BCC Research

The energy (biofuels) market was $249.9 million in 2016 and is forecast to grow at a CAGR of 23.4% to reach a value of $714.3 million by 2016. Enabled products make up the bulk of this market, and include butanol, diesel, ethanol and other fuels such as jet fuel.

Biofuels markets are affected by several forces, including government regulations, prices of fossil-derived fuels and feedstock costs. In recent years, the declining price of crude oil has exerted a large influence on the biofuels industry. Crude oil prices declined from a high of $102/barrel in September 2013 to $44/barrel in September 2016. Because biofuels must compete with fossil fuels, a price decline reduces profits, puts pressure on biofuels producers and dampens enthusiasm for new capacity.

These trends have resulted in a recent shakeout in the industry, with fewer producers staying in this market. However, despite the recent crude oil price headwinds, the biofuels market is projected to continue to grow primarily due to existing and planned mandates in many countries that provide for advanced biofuels consumption, existing and planned plant capacities, continued enthusiasm in Europe for biodiesel, growth in biobutanol as a transportation fuel and growth of specialty fuel applications (e.g., iso-octane in two- and four-stroke engines).

In particular, next-generation biofuels will drive demand through 2021. These fuel types include renewable diesel, jet biofuel, butanol and biocrude. Increasing use of novel feedstocks, including agriculture residues, energy crops, waste oils and carbon dioxide, is also a key trend for this industry. These energy trends (novel fuels and feedstocks) are advanced by synthetic-biology platforms, and thus this industry will see strong growth through 2021.

The expansion of biofuels into new market sectors, including aviation, maritime transport, electricity generation and cooking energy, is also contributing to the market growth.

AGRICULTURE MARKET

The global value of the synthetic-biology agriculture market, by product type, is shown in the table below. Synthetic biology has the potential for improving the world’s food and

livestock systems. There is a significant need for better ways to produce high-quality and safe foods and feeds. Synthetic biology provides unique processes and tools for meeting these needs.

TABLE 75

GLOBAL VALUE OF AGRICULTURE MARKET, BY PRODUCT TYPE, THROUGH 2021 ($ MILLIONS)

Product Type	2015	2016	2021	CAGR% 2016–2021
Enabling products	13.8	15.7	315.9	82.3
Biologic components	10.2	11.7	55.1	36.3
Integrated systems	0.1	0.4	47.4	159.9
Enabled products	5.9	7.6	578.5	137.8
Total	30.0	35.4	996.9	95.0

Source: BCC Research

The synthetic-biology agriculture market was $35.4 million in 2016, and is growing at a high CAGR of 95.0% to reach a market size of $996.9 million in 2021.

Enabling products and biologic components comprised a majority of this market in 2016, with enabled products becoming very important by 2021. The agriculture industry is beginning to use synthetic biology to develop better seeds that provide highly desirable traits such as disease protection, drought resistance and pesticide resistance. Also, for animals, synthetic-biology tools are becoming more useful for breeding and lowering the incidence of diseases among animals.

The agriculture enabled products market was $7.6 million in 2016 and is growing at a rapid rate of 137.8% to reach a forecast value of $578.5 million by 2021. Enabled products in 2016 include pest-control systems (marketed by Oxitec) and non-GMO canola seeds (Cibus). These products have been introduced only recently into the market.

It is forecast that both of these agricultural applications will continue to grow and diversify during the next five years, and animal applications will come on stream as well. For example, Dow AgroScience’s next generation of Smartstax products (multigene traits) will use genome-editing technologies. Cellectis is working on a wide range of new seed products that will use genome editing. Several companies are using synthetic-biology tools for animal applications; these companies include Recombinetics (dairy and beef cattle) and BGI Shenzhen (engineered micropigs).

SYNTHETIC-BIOLOGY MARKET BY PRODUCT TYPE

The table below summarizes the value of the synthetic-biology market by product type.

TABLE 76

GLOBAL VALUE OF SYNTHETIC--BIOLOGY MARKET, BY PRODUCT TYPE, THROUGH 2021
($ MILLIONS)

Product Type	2015	2016	2021	CAGR% 2016–2021
Enabled products	2,593.5	2,800.6	8,336.8	24.4
Enabling products	692.3	786.0	1,914.5	19.5
Biologic components	196.5	227.7	491.6	16.6
Integrated systems	66.0	83.8	667.1	51.4
Total	3,548.3	3,898.1	11,410.0	24.0

Source: BCC Research

Enabling products include DNA synthesis and assembly, genome editing, informatics, DNA sequencing and specialty media. The market for enabling products was $786.0 million in 2016, and is growing at a CAGR of 19.5% to reach a market size of over $1.9 billion in 2021.

The biologic components market includes synthetic genes (both standardized and value added), plasmid delivery vehicles and BioBrick parts. The market for biologic components was $227.7 million in 2016, and is growing at a CAGR of 16.6% to reach a market size of $491.6 million in 2021.

Integrated systems include production systems (i.e., cell factories based on synthetic biology enzyme and microbial systems), synthetic chassis organisms (i.e., microorganisms containing minimal genomes) and synthetic cells. The market for integrated systems was $83.8 million in 2016, and is growing at a CAGR of 51.4% to reach a market size of $667.1 million in 2021.

Enabled products include products for which synthetic-biology tools play an enabling role in either their discovery or production. The market for enabled products was just over $2.8 billion in 2016, and is growing at a CAGR of 24.4% to reach a market size of over $8.3 billion in 2021.

Enabled products constitute a majority of the 2016 synthetic-biology market, and represent value-added opportunities for companies in this industry. Downstream products produced by synthetic biology can capture high market volume and thus are a key target for many companies. This gives incentives for core technology providers (e.g., biologic components or integrated systems) to capture this value through strategic alliances with downstream producers.

Examples of this trend can be seen by several alliances formed in 2016, including LanzaTech/Aemetis (biofuels), Intellia Therapeutics/Regeneron Pharmaceuticals (therapies), Ginkgo/Amyris (cosmetics, jet fuel and lubricants) and Givaudan/ Amyris (fragrances).

The key reasons for alliance-building in the synthetic-biology industry vary, based on the specific end market. In the case of energy and chemicals, engineering, bioprocessing and distribution skills are required. In the case of pharmaceuticals, GMP manufacturing and regulatory skills may be required.

Each of the market segments in the table – enabling products, biologic components, integrated systems and enabled products – require unique skill sets to be successful.

Companies selling enabling products must be skilled in DNA synthesis, bioinformatics, genomics, proteomics and/or molecular biology. Companies supplying enabling product technologies are typically life science tool companies. The situation is similar in the biologic components market, although more skills are required in applied disciplines including gene assembly, protein expression and cloning.

Suppliers of integrated systems require high levels of expertise in downstream biotechnologies, including pathway engineering, directed evolution, cloning and protein expression.

Companies producing enabled products require broad skills in chemical and biochemical engineering and unit processes such as fermentation, distillation, separations and pretreatment, among others.

Based on these technical requirements, few companies participate across the full range of synthetic-biology markets.

ENABLING PRODUCTS MARKETS

The table below gives the value of synthetic biology enabling products, including DNA synthesis and assembly, genome editing, informatics, DNA sequencing and specialty media.

TABLE 77

GLOBAL VALUE OF ENABLING PRODUCTS, BY PRODUCT TYPE, THROUGH 2021 ($ MILLIONS)

Product Type	2015	2016	2021	CAGR% 2016–2021
Genome editing	456.6	503.3	849.2	11.0
DNA synthesis and assembly	105.0	121.4	393.9	26.5
DNA sequencing	60.8	75.1	241.7	26.3
Informatics	55.1	66.9	289.6	34.1
Specialty media	14.8	19.3	140.1	48.7
Total	692.3	786.0	1,914.5	19.5

Source: BCC Research

The 2016 market for enabling products was $786.0 million and is forecast to grow at a 19.5% annual rate to reach a market size of $1.9 billion in 2021.

Genome editing is a key enabling technology for synthetic biology, and the size of this market was $503.3 million in 2016, and it is growing at a CAGR of 11.0% to reach a forecast value of $849.2 million by 2021.

The genome-editing market growth is being driven by the advent of new technologies such as CRISPR/Cas9, and by increasing market demand primarily in the research, pharmaceuticals and agriculture industries. In the research market, genome editing is used for a number of genetic manipulations including knock-outs, knock-ins, tag-ins, chromosomal rearrangements, transcriptional interference, and activation and genetic screening.

In agriculture, genome editing can be used for breeding and reducing the disease burden in animals and for developing novel germplasm for seeds. Advantages for seed development are that it can introduce multiple traits simultaneously, such as resistance to pests, diseases and herbicides.

Genome editing is an enabling technology for a range of therapeutic applications. Applications include genes with autosomal function including autoimmune and blood disorders, cancers and other gene-based diseases. There is much R&D underway for applications in these monogenic diseases. Genome editing also is promising for multiple allele diseases, for example, cystic fibrosis.

DNA sequencing includes sequencing for quality control in the manufacture of biologic parts but does not include sequencing used in genomics research to build gene databases. This latter application is large and assists synthetic biology; however, it is very difficult to assign specifically to the industry and so is excluded. Sequencing accounted for $75.1 million in 2016, and is growing at a CAGR of 26.3% to reach a forecast size of $241.7 million by 2021.

DNA sequencing is growing due to the need for sequencing to verify the sequence information for genes and other DNA constructs that are synthesized for synthetic-biology applications. This step is essential for assessing the quality of the final DNA product and to verify that it matches the original specifications.

Bioinformatics technologies provided in the form of products and services are a key enabling technology for biologic components and integrated systems. The market for bioinformatics is benefitting from a shift toward more complex synthetic genes and biologic parts and the resultant need for more sophisticated design capabilities. Software that enables design of longer DNA sequences is particularly high in demand.

Synthetic-biology companies use bioinformatics to differentiate their products and to create competitive advantage, and in many cases the full value is not realized in direct sales to customers, but in increased sales of the biologic part itself.

DNA synthesis is critical to many aspects of synthetic biology, including constructing genetic building blocks, long DNA sequences, synthetic genes and gene clusters, minimal

genomes, gene libraries and chassis organisms. The value of DNA synthesis and assembly products is forecast to grow from $121.4 million in 2016 to $393.9 million by 2021.

Specialty media are important to synthetic biology because they ensure the viability of cellular biofactories. Specialty media consist of cell culture media, reagents and sera for viability and growth of synthetic biology cell factories. These products are higher-value media, specifically designed for synthetic-biology applications to ensure that they work in the intended applications

The growth in the specialty media market is driven by increasing demand for cell-based synthetic-biology production systems. BCC Research forecasts that the specialty media market will grow at a CAGR of 48.7% to reach a market size of $140.1 million by 2021.

The table below shows the value of the enabling products, by industry. The primary consuming industries for these products include agriculture, chemicals, energy, pharmaceuticals and research.

TABLE 78

GLOBAL VALUE OF ENABLING PRODUCTS, BY END-USE INDUSTRY, THROUGH 2021
($ MILLIONS)

Industry	2015	2016	2021	CAGR% 2016–2021
Pharmaceuticals	443.1	503.1	957.3	13.7
Research	152.3	172.9	287.2	10.7
Chemicals	62.3	70.7	277.6	31.5
Energy	20.8	23.6	76.5	26.5
Agriculture	13.8	15.7	315.9	82.3
Total	692.3	786.0	1,914.5	19.5

Source: BCC Research

The primary end-user segments in 2016 were pharmaceuticals and research, with market values of $503.1 million and $172.9 million, respectively.

The research and pharmaceuticals industries perform a significant amount of R&D using synthetic-biology platforms, and they are key focus industries for enabling-technology providers. The pharmaceutical industry is a large user of DNA-synthesis, DNA-sequencing and genome-editing technologies, as these are key tools in the discovery and development of new drugs and therapies.

Applied markets, including chemicals, energy and agriculture, perform less fundamental and applied research in synthetic biology, but they will be consuming enabling technologies as they scale-up commercial processes in the future.

In particular, agriculture is projected to be a large consumer of enabling tools, for a range of applications including animal breeding, reducing diseases in animals and seed

development. Based on these market needs, the market for enabling tools in the agriculture industry is projected to grow at a high CAGR of 82.3% to reach a forecast level of $315.9 million by 2021.

BIOLOGIC COMPONENTS MARKET

The table below gives the value of the biologic components market, by product type, through 2021.

TABLE 79

GLOBAL VALUE OF BIOLOGIC COMPONENTS MARKET, BY PRODUCT TYPE, THROUGH 2021
($ MILLIONS)

Product Type	2015	2016	2021	CAGR% 2016–2021
Value-added genes	87.7	100.8	271.2	21.9
Standardized genes	71.8	82.4	90.4	1.9
Delivery (plasmids)	23.1	27.5	75.9	22.5
BioBrick parts	13.9	17.0	54.1	26.1
Total	196.5	227.7	491.6	16.6

Source: BCC Research

The value of the biologic components market was $227.7 million in 2016, and is growing at a CAGR of 16.6% to reach a forecast value of $491.6 million by 2021.

The biologic components market includes synthetic genes (both standardized and value added), plasmid delivery vehicles and BioBrick parts. The market for these products is growing due to their central role in synthetic biology as building blocks for integrated systems and in cellular factories for enabled products. Markets where synthetic biology is emerging, for example, China, are also contributing to the future growth.

Also contributing the growth in this market segment are organizations that are developing synthetic-biology products, thus spurring demand. These organizations include BioBricks, DIYbio and SynBERC, among others.

Biologic components have not yet reached commodity status, but are rapidly decreasing in costs. These products represent value-added opportunities for DNA-synthesis companies, and many have entered the synthetic-gene market as a result. However, this industry is very consolidated with the top five companies holding approximately 70% of the global market share.

Synthetic genes are an important part of the biologic components market. The synthetic-gene market consists of three segments: standardized, value-added academic and value-added industrial. Specialization in a given market segment allows the gene-synthesis companies to differentiate and maximize their market potential. In 2016,

the market for standardized genes was $82.4 million, and the market for value-added genes was $100.8 million.

The value-added, custom synthetic-gene market is growing at a rapid rate and is forecast to reach $271.2 million by 2021. The value-added gene segment has been influenced in the past by large orders from U.S. government agencies, including the NIH, for complex synthetic genes.

Synthetic-Gene Standardized Market Segment

Standardized genes represent the low-cost market segment. In this segment, the customer typically orders from one to 50 standard genes, and delivery time is critical. Typical order sizes in this category can range from $500 to $50,000. The length of standardized genes can range from a few to tens of thousands base pairs (bp).

Synthetic-Gene Value-Added Market Segment

High-value-added market segments include two customer types: academic/ government and industrial. These products are long length, and often complex, DNA components (e.g., large genes and functionalized gene clusters), specialty genes (e.g., RNA-interference-resistant genes) or gene clusters. The length of specialized genes can be up to 150,000 bp.

Academic customers demand larger constructs, often in the thousands of kilobases. Delivery time is not as critical to these customers. Industrial customers are time sensitive and delivery is a purchasing factor. Length of the DNA construct for industrial users is usually smaller than that of academic customers, often in the hundreds of kilobase range.

BioBrick parts include zinc finger protein gene-control circuits, promoter and terminator sequences, repressor genes, reporter genes, cell–cell signaling sequences, genetic switches, conjugation parts and cell-death sequences. BioBrick parts are a rapidly growing segment (26% annual growth rate through 2021) of the biologic components market and represent an attractive opportunity for DNA-synthesis companies to capture market share in a value-added segment of the business.

While BioBrick parts make up a relatively small portion of the projected market in 2021 – $54.1 million out of $491.6 million total components market – they represent a strategic product for synthetic-biology applications, and companies that perform well in this business are well positioned among lead users in academia and industry.

The table below shows the global value of the biologic parts market by end-user industry.

TABLE 80

GLOBAL VALUE OF BIOLOGIC COMPONENTS MARKET, BY END-USER INDUSTRY, THROUGH 2021
($ MILLIONS)

End-User Industry	2015	2016	2021	CAGR% 2016–2021
Pharmaceuticals	119.8	140.5	285.1	15.2
Research	55.0	62.1	113.1	12.7
Agriculture	10.2	11.8	55.1	36.1
Chemicals	7.6	8.8	29.0	26.9
Energy	3.9	4.5	9.3	15.6
Total	196.5	227.7	491.6	16.6

Source: BCC Research

The pharmaceuticals market is quite significant, with a value of $140.5 million in 2016 and a CAGR of 15.2% to reach $285.1 million by 2021. Research is also a significant market segment, with a value of $62.1 million in 2016 and growing at a CAGR of 12.7% to reach $113.1 million by 2021.

For the pharmaceuticals and research market segments, strong growth drivers are the need for standardized and custom synthetic genes, plasmids and associated BioBrick parts. The R&D of new medicines requires testing of a large number of synthetic genes to evaluate efficacy and safety. This work is done at universities and research facilities at large pharmaceutical companies. The workflow involves designing the gene at the research facility and then sending the coding information to synthetic-gene companies that make the gene. The gene is delivered using plasmids, contributing to growth in these products.

The mass production of a gene once it has been synthesized can be done with well-characterized plasmid vectors (e.g., bacteria, ovaries, plants, animals), which copy the original gene that was synthesized. Assessing the final product and its fidelity to the desired specification is done with next-generation sequencing instruments.

The agriculture and chemicals market segments have high growth rates through 2021. Both the agriculture and chemicals markets are increasing being driven by an increasing use of molecular-biology tools to develop new products, such as novel seeds or specialty chemicals. This drives the demand for DNA-synthesis products and plasmids. In agriculture, testing of new genes is important as part of the seed development process. For chemicals, synthetic genes are needed for developing and optimizing new synthetic-biology-based microbial production processes.

INTEGRATED SYSTEMS MARKET

The table below shows the global value of the integrated systems market by end-user industry. Integrated systems include production systems (i.e., cell factories based on

synthetic biology enzyme and microbial systems), synthetic chassis organisms (i.e., microorganisms containing minimal genomes) and synthetic cells.

TABLE 81

GLOBAL VALUE OF INTEGRATED SYSTEMS MARKET, BY TYPE, THROUGH 2021 ($ MILLIONS)

Type	2015	2016	2021	CAGR% 2016–2021
Production systems	51.9	67.2	541.9	51.8
Chassis organisms	14.1	15.2	43.4	23.3
Synthetic cells	–	1.4	81.8	125.6
Total	66.0	83.8	667.1	51.4

Source: BCC Research

The total value of integrated systems in 2016 was $83.8 million, and is growing at a CAGR of 51.4% to reach a forecast value of $667.1 million by 2021.

The market for chassis organisms is forecast to grow from $15.2 million in 2016 to $43.4 million by 2021. While this market segment is still emerging, it offers great potential for future growth. A chassis organism is one whose genome has been altered using synthetic-biology techniques to give it new, useful properties.

Scarab Genomics, a leading company in this market segment, has developed a chassis organism based on *E. coli*. Scarab has synthetically engineered a strain of *E. coli*, called Clean Genome, which contains only essential genes. The applications for this type of an organism include cloning and as a cellular factory that has improved genetic stability as well as high metabolic efficiency.

Merial, a leading animal-health company, has developed and introduced on the market a therapeutic vaccine for canine melanoma, called Oncept, by utilizing Scarab’s chassis organism.

The synthetic cells market is still emerging, with the first products launched in 2016 by SGI-DNA, to the research markets. The market in 2016 was $1.4 million and is forecast to reach a size of $81.8 million by 2021.

Researchers from SGI-DNA’s parent company, Synthetic Genomics, completed the construction of the first minimal synthetic bacterial cell, JCVI-Syn3.0, in March 2016. This accomplished the goal of building a minimal operating system for a cell, which could be used for research and industrial applications.

SGI-DNA markets these minimal cells under the Syn2.0 and Syn3.0 Minimal Synthetic Cells trade names. Research applications include determining essential gene function, use as models for generating other organisms and functioning as a chassis for manipulating genetic and/or metabolic pathways.

The Syn3.0 cell marks a departure from other synthetic cells that have been made since 2010. To make the first synthetic cell in 2010, researchers took an existing bacterial genome and inserted it into another cell. The 2016 minimal cell was constructed from the bottom up by building the genome from scratch, and it can be considered to be a new, artificial species.

The market for production systems was $67.2 million in 2016 and is forecast to reach $541.9 million by 2021. Growth will come from the commercialization of both microbial and enzyme production systems.

Microbial production systems have tremendous potential for producing a range of products.

For example, several companies are developing algae-based synthetic-biology production systems, including Algenuity and Triton Algae. These production platforms can be used to enable products in a range of downstream industries, including biofuels, chemicals and pharmaceuticals.

Enzyme systems using synthetic biology are also becoming important as cell factories.

For example, Novozyme is the largest supplier of enzymes to the U.S. bioethanol industry; these enzymes are used to produce second-generation bioethanol from agricultural residues.

Several companies, including Zymergen and Ginkgo, are involved with designing and developing synthetic-biology factories that use microbes to produce chemicals and other products. These companies specialize in organism design, and scale-up of the redesigned organism.

These synthetic-biology factories are being designed to meet a growing demand for sourcing plant-derived extracts such as nutraceuticals, flavors, fragrances, and sweeteners from systems employing engineered microbes. In order to meet this demand, there is an emphasis on rapid design and scale-up of different organism lines in a low-cost way. Skills required include organism design, build and testing and involve such advanced technologies as computer-aided design software, low-cost gene synthesis and highly accurate mass liquid chromatography mass spectrometry.

The table below shows value of the integrated systems market, by end-user industry, through 2021.

TABLE 82

GLOBAL VALUE OF INTEGRATED SYSTEMS, BY END-USER INDUSTRY, THROUGH 2021
($ MILLIONS)

Industry	2015	2016	2021	CAGR% 2016–2021
Pharmaceuticals	27.2	34.3	278.1	52.0
Chemicals	23.0	30.0	219.2	48.8
Research	12.0	13.9	83.9	43.3
Energy	3.7	5.2	38.5	49.2
Agriculture	0.1	0.4	47.4	159.9
Total	66.0	83.8	667.1	51.4

Source: BCC Research

Early adopters of integrated systems are R&D laboratories that are working out synthetic-biology strategies and that have the technologies required (e.g., gene synthesis, DNA-sequencing instruments) for studying new systems. The research market segment was valued at $13.9 million in 2016, and is forecast to grow at a CAGR of 43.3% to reach $83.9 million by 2021.

The chemicals and pharmaceuticals industries are also key users of integrated systems. The value of these systems in the chemicals market was $30.0 million in 2016 and is growing at a CAGR of 48.8% to reach $219.2 million in 2021. Likewise, the pharmaceuticals market reached a value of $34.3 million in 2016 and is growing at a CAGR of 52.0% to have a forecast value of $278.1 million by 2021.

The use of novel production processes based on synthetic biology is important to the pharmaceutical industry, as evidenced by the above-mentioned use of a chassis organism by Merial in its canine melanoma vaccine development program.

Ginkgo Bioworks, a leading company in production systems, has made a strategic effort to design and scale-up production systems for the pharmaceuticals industry. Another leading company in this space, Zymergen, has drug companies as its clients and is developing production systems for making generic pharmaceuticals.

Agriculture is an emerging, but fast-growing end-user industry for these systems. For agricultural applications, the engineered organism must be compatible with the downstream applications.

In addition, the growth in agriculture is being driven by the need to replace traditional chemicals with microbial-based inputs. This is evidenced by several agricultural biotechnology companies' focus on producing pesticides and fertilizers using microbial methods; these companies include Adaptive Symbiotic Technologies, AgBiome and Indigo. Zymergen has a strong interest in this end-user segment.

ENABLED PRODUCTS MARKET

SOURCES OF COMPETITIVE ADVANTAGE

Synthetic biology has a key commercial impact in applied markets, including biofuels, chemicals, pharmaceuticals and agricultural industries. One of the reasons for its importance in these industries is that synthetic biology allows for increased performance, often at lower costs. This provides competitive advantage in the marketplace.

Examples of enhanced commercial performance of synthetic-biology-enabled products are given in the following two tables. These examples illustrate the nature of the competitive advantage and commercial incentives for implementing synthetic biology.

The first table below compares three biodiesel fuel types – petroleum diesel, biodiesel and synthetic-biology-derived diesel – across several performance measures. The second table compares two drug-production methods – plant based and synthetic biology microbial based – by cost and production times.

In both of these cases, synthetic-biology-derived methods perform better than conventional technologies on a cost and performance basis.

TABLE 83

BIODIESEL FUEL PERFORMANCE COMPARISON

Fuel Type	**Cloud Point** (°C)	**Cetane Number**	**Energy Density** (1,000 Btu/Gallon)
Petroleum diesel	–9 to –30	40 to 55	115 to 142
Biodiesel*	+1	47	118
Farnesene diesel*	< –50	58.6	123

*Synthetic biology.
Btu, British thermal unit.

Source: BCC Research

The cloud point is the temperature below which wax forms a cloudy appearance. The lower the number the better, since wax solids can thicken the oil, clogging fuel filters and injectors in engines.

The cetane number measures a fuel’s ignition delay. A high cetane number gives a lower ignition delay.

The energy density is the amount of energy stored in the fuel per unit volume and determines the fuel efficiency (e.g., miles per gallon). The higher this number is, the better the fuel efficiency.

On each of these three performance measures, bio- and farnesene-diesel show superior values compared with conventional petroleum-based diesel.

The table below compares artemisinin drug production for natural and microbial (synthetic biology) methods.

TABLE 84

ARTEMISININ DRUG PRODUCTION COMPARISON

Production Method	Production Cost ($/dose)	Production Time (Months)
Natural plant	2.40	14.0
Microbial*	0.25	0.5

*Synthetic biology.

Source: BCC Research

The overall cost savings by using synthetic-biology-produced artemisinin can be estimated at $2.15 per dose at 500 million doses, or $1 billion. This represents a significant advantage over current production methods.

A third example of competitive advantage is in the artificial sweetener industry and is an example of value added.

The table below compares the traditional method of producing Stevia, a food sweetener, through natural extraction, and the synthetic-biology method.

TABLE 85

SWEETENER PRODUCT COMPARISON

Product	Main Ingredient	Aftertaste
Stevia	Reb A	Bitter
EverSweet*	Reb D, Reb M	Sweet

*Synthetic biology.

Source: BCC Research

In the case of stevia, it is today extracted from a leafy green plant native to South America. The sweetness comes from a family of compounds called rebaudiosides (e.g., Reb A, Reb D, etc.). Reb A is the most common compound produced by the leafy plant, but it becomes bitter in too high a quantity. Reb D and Reb M are sweeter, but they are not present in high concentrations in the plant, so it is expensive to extract in high quantity for sweeteners.

Using synthetic-biology platforms, Evolva has engineered the yeast genome to produce mostly Reb D and Reb M, which is sweeter and more suitable for drinks and other foods.

The above examples illustrate key reasons why the enabled products market is a key growth opportunity for the synthetic-biology industry.

The table below summarizes the global value of synthetic-biology-enabled products, by end-user industry, from 2016 through 2021.

TABLE 86

GLOBAL VALUE OF ENABLED PRODUCTS MARKET, BY END-USER INDUSTRY, THROUGH 2021
($ MILLIONS)

End-User Industry	2015	2016	2021	CAGR% 2016–2021
Pharmaceuticals	1,253.5	1,326.1	3,838.5	23.7
Chemicals	1,147.7	1,250.3	3,329.9	21.6
Energy	186.4	216.6	589.9	22.2
Agriculture	5.9	7.6	578.5	137.8
Research	–	–	–	–
Total	2,593.5	2,800.6	8,336.8	24.4

Source: BCC Research

The market for enabled products is forecast to grow from $2.8 billion in 2016 to $8.3 billion by the year 2021, a 24.4% CAGR. This growth reflects the importance of the synthetic-biology value chain, with downstream, enabled products capturing significant portions of the value.

Synthetic biology is becoming an important industrial biotechnology platform with robust and growing market applications.

The pharmaceutical industry accounted for over $1.3 billion in 2016 and is forecast to grow at a CAGR of 23.7% to reach over $3.8 billion by 2021. In the pharmaceuticals industry, the majority of 2016 sales were made of drugs produced by synthetic-biology platforms, including cephalosporin (DSM), artemisinin (Huvepharma), Januvia (Merck) and vaccines (Seqirus).

The chemical industry will experience significant growth in products during the next five years. The chemical industry accounted for over $1.2 billion in 2016 and is forecast to grow at a CAGR of 21.6% to reach over $3.3 billion by 2021. The main products produced in 2016 in the chemicals industry were PDO, an intermediate for the polymer Sorona (DuPont), and biosuccinic acid (various producers) and squalene (Amyris). Other specialty chemicals (e.g., food ingredients, surfactants and cosmetics) make up the balance of this market.

The energy industry accounted for $216.6 million in 2016 and is forecast to grow at a CAGR of 22.2% to reach $589.9 billion by 2021. The energy industry consists of biofuels, including butanol, diesel, ethanol and other specialty fuels such as jet fuel. This market is influenced by government mandates and incentives, as well as the price of oil.

Aggressive government mandates for biofuels blending are in place in the major counties throughout the world. As a result, demand for biofuels will continue to be high, despite the drop in oil prices from 2011 through 2016.

Synthetic-biology platforms are important in biofuels production, and multiple companies are pursuing this market. These companies include Aemetis, Algenol, BASF/Verenium, Beta Renewables, DSM/Poet, DuPont, Iogen and OPX Biotechnologies.

The agriculture industry accounted for $7.6 million in 2016 and is forecast to grow at a CAGR of 137.8% to reach $578.5 million by 2021.

The agriculture market consists of three main segments: animals, pest control, and seeds. The animals market segment is influenced by the need for more disease-resistant livestock (e.g., genetically edited pigs) and more efficient breeding of beef animals and dairy cattle.

The seed market is being driven by the rise of new genome-editing technologies such as CRISPR/Cas9 systems. These methods are being used to engineer desirable traits and/or resistance traits into crop plants.

The pest-control market is driven by the need for more effective ways to control mosquitoes, particularly to meet outbreaks such as the recent Zika virus outbreak.

PHARMACEUTICALS MARKET

The pharmaceuticals market is quite significant for synthetic biology, with a size of over $1.3 billion in 2016. The market is growing at a CAGR of 23.7% and is forecast to reach a size of over $3.8 billion by 2021.

TABLE 87

GLOBAL VALUE OF ENABLED PHARMACEUTICALS MARKET, BY DRUG CLASS, THROUGH 2021
($ MILLIONS)

Drug Class	2015	2016	2021	CAGR% 2016–2021
Diabetes	689.4	729.1	2,576.4	28.7
Antibiotics	449.7	464.1	543.2	3.2
Vaccines	108.8	126.9	667.1	39.4
Malaria	5.6	6.0	27.6	35.7
Other	–	–	24.2	–
Total	1,253.5	1,326.1	3,838.5	23.7

Source: BCC Research

Antibiotics consist of third- and fourth-generation cephalosporin drugs. The value of synthetic-biology-derived antibiotics was $464.1 million in 2016, and is growing at a CAGR of 3.2% to reach a forecast value of $543.2 million by 2021.

The overall global market for cephalosporins (beta lactams) is very large, approximately $11 billion, and is growing at a high single digits per year rate. The market is growing due to rise in infectious diseases across the globe, emerging infectious diseases and a gap in the supply and demand for antibiotics.

Cephalosporins are antibacterial antibiotics, and they inhibit synthesis of the bacterial cell wall. They are broad spectrum antibiotics and can be grouped into five generations according to their antimicrobial properties. Each successive generation provides an increase in gram-negative antimicrobial properties, with the third- to fifth-generation products being the most effective.

Higher-generation cephalosporins require a more specialized and complex production process; for example, they require a dedicated production line. Thus, a cephalosporin plant cannot manufacture another active pharmaceutical ingredient. This means higher barriers to entry and higher margins.

The main competition for cephalosporins is producers in India and China, and efficient production methods are a competitive differentiator. DSM Sinochem Pharmaceuticals (a joint venture formed in 2011 between DSM and Sinochem [China]) makes a PureActives product line for high-quality penicillin and semisynthetic cephalosporins. The company uses synthetic-biology methods for developing manufacturing technologies such as novel enzymes. Products covered under this platform include Purimox (amoxicillin trihydrate), Purilex (cephalexin) and Puridrox (cefadroxil).

DSM Sinochem is emphasizing the growing market in China for cephalosporins. The company built a plant in 2013 that manufactures synthetic cephalosporins using synthetic-biology-based processes. The plant is able to achieve significant savings in energy consumption, waste disposal and industrial air emission through its unique enzyme manufacturing technology.

The value of synthetic-biology-derived diabetes drugs was $729.1 million in 2016, and is growing at a CAGR of 28.7% to reach a forecast value of just under $2.6 billion by 2021. The main drugs include Januvia and Janumet, which are used to treat Type 2 diabetes.

Merck, working with Codexis, developed a synthetic-biology-based method for manufacturing the drug Januvia. Januvia is a new treatment for Type 2 diabetes that was approved in 2006. Sitagliptin, a chiral beta-amino acid derivative, is the active ingredient in Januvia and Janumet.

The first-generation synthesis for sitagliptin required eight steps including several aqueous workups. It also required high-molecular-weight chemicals that did not end up in the final molecule and therefore were waste.

Merck and Codexis developed a biosynthetic route to making sitagliptin that could potentially increase the yield by up to 15%, reduce the use of rhodium and significantly reduce the waste byproducts.

In December 2015, Merck executed an extension agreement with Codexis for supply of a proprietary enzyme used in the manufacturing process for sitagliptin.

The value of synthetic-biology-derived malaria drugs, semisynthetic artemisinin, was $6.0 million in 2016, and is growing at a CAGR of 35.7% to reach a forecast value of $27.6 million by 2021.

The small molecule artemisinin is a naturally occurring compound used to treat multiresistant forms of malaria. The naturally occurring form of artemisinin is currently too expensive for most people in developing countries where malaria occurs.

Over a four-year period, Dr. Jay Keasling and Amyris used synthetic-biology tools to develop a process for producing synthetic artemisinin at a cost that it significantly less than its natural counterpart. The genes for the enzymes that produce artemisinin were identified in the artemesia genome, and transferred to a yeast genome. A total of twelve genes were transferred. Constructs for controlling the expression of these genes were also added to the yeast genome. Using the new process, the drug can be produced by the yeast in a bioreactor.

The entire process was transferred to Sanofi-Aventis in 2013, and that same year, the first commercial semisynthetic artemisinin factory was started up in Garessio, Italy.

Artimisinin, which is used as an active ingredient in artimisinin combination therapies (ACTs), is traditionally sourced from the sweet wormwood plant. Because it is supplied from agriculture sources, the supply is erratic and prices vary from year to year. Semisynthetic artemisinin offered the hope of stabilizing the market.

A price decline in agricultural artemisinin during 2014 and 2015 (average price went to $250/kilogram) meant that it was no longer profitable to produce the semisynthetic version (breakeven pricing is estimated to be $350/kilogram to $400/kilogram).

Sanofi requires artemisinin for its own ACT therapeutics, but demand for ACT itself was also evening off during this time due to a trend of better diagnosis of malaria prior to giving treatments. ACT had previously been given to all patients with fever, including many who did not have malaria.

Based on these industry and market factors, Sanofi decided to sell its semisynthetic artemisinin factory to Huvepharma in 2016. Huvepharma produces artemisinic acid, a precursor to artemisinin, via yeast fermentation. This acquisition by Huvepharma allows the company to control the overall semisynthetic artemisinin value chain. A key factor in the future success of semisynthetic artemisinin will be the ability to bring its production costs in line with the market price for natural artemisinin.

The acquisition of this factory by Huvepharma will help to stabilize the supply of semisynthetic artemisinin, as Huvepharma controls much of the value chain in the overall production of the drug. It is hoped that production of semisynthetic artemisinin will have several market benefits. For the first time, the drug will be widely available. It will benefit patients who are being hurt by the current artemisinin counterfeit market, which increases drug resistance risk. Synthetic artemisinin will also counter speculators who hoard stocks of the natural plant, which further increases drug prices.

The value of synthetic-biology-derived vaccines was $126.9 million in 2016, and is growing at a CAGR of 39.4% to reach a forecast value of $667.1 million by 2021. Influenza vaccines are particularly being impacted by synthetic biology.

At the onset of a new flu outbreak, vaccine manufacturers receive samples of the new flu strain from government agencies. In turn, the vaccine manufacturer grows large numbers of the pathogen in chicken eggs, to prepare the seed-starting material for vaccines. This process takes many weeks, thus limiting the ability to respond quickly to new outbreaks.

Due to these issues, there is a strong market need for a production platform that could provide just-in-time regional vaccine supplies. The goal would be to have a flexible, portable vaccine production method that could respond in time to pandemics as well as seasonal demand and reduce mismatches in local or global vaccine supply and demand.

Novartis, working with the J. Craig Venter Institute, the Centers for Disease Control and Synthetic Genomics Vaccines, developed a method to chemically synthesize the virus genomes and grow them in tissue culture cells. This process enables a vaccine manufacturer to save significant time and money to produce a new vaccine in response to a flu outbreak. Novartis' product, Flucelvax, began shipping to the U.S. for the 2013 and 2014 flu season. Approximately 30 million doses were shipped in 2013.

In July 2015, the CSL Group acquired the influenza vaccines business of Novartis in the U.S. This business was integrated into CSL's influenza vaccine business and now operates as Seqirus. Flucelvax and Flucelvax Quadrivalent have been approved by the FDA and are manufactured in Holly Springs, N.C.

"Other" synthetic-biology-enabled drugs besides those discussed above include genome-edited drugs. Some genome-edited drugs are in clinical trials, but these are not expected to make a significant contribution to 2021 sales.

It is possible that drugs based on ZFN and CRISPR/Cas9 technologies may be launched by 2021, with initial sales in that year. This is reflected in the forecast. ZFN-based drugs that may emerge by 2021 include for hemophilia and HIV, and these are being developed by Sangamo Therapeutics. CRISPR/Cas9-based drugs that may emerge during this time include those for eye diseases, and these are being developed by Editas Medicine.

CHEMICALS MARKET

The conversion of the chemical industry to synthetic-biology-based production processes is an emerging process, and this will require some time. Many of the first applications of chemicals involve high-value chemical products, including polymers, cosmetics and flavors and fragrances. This is because bioprocessing is always compared with conventional chemical processing when deciding a production process.

Considerations such as those given in the table below are important when making this decision.

TABLE 88

FACTORS FOR SYNTHETIC-BIOLOGY-BASED CHEMICAL PROCESSES

Factor	Conventional Chemical Process	Synthetic Biology Process
Reaction time	Fast (hours)	Slow (days)
Feedstocks	Petroleum based	Agriculture based
% feedstock to product	High (90+ %)	Low (30% to 60%)
Reaction matrix	Organic solvents	Water
Reaction conditions	High temperature, pressure	Low temperature, pressure
Product recovery	High concentration, low–moderate cost	Low concentration, high cost

Source: BCC Research

The main advantages bioprocesses have over conventional chemical processes are mild reaction conditions (i.e., low temperature and pressure), avoidance of organic solvents and use of renewable agricultural feedstocks. The main disadvantages include slower reaction times, lower product conversion rates and more difficult and costly product recovery.

Conventional chemical production processes are very competitive and difficult to displace. Synthetic-biology tools can be used to improve the weaknesses of bioprocessing relative to conventional chemical processes.

For example, synthetic biologists work to improve the production microorganism to give better performance by methods such as the following: minimizing the microorganism’s genome (resulting in faster growth); incorporating cell pathways for metabolizing a range of feedstocks; removing unneeded pathways that consume feedstocks (thus increasing the conversion of feedstock to product); constructing production organisms that can produce multiple products; and developing better control of the bioprocess (by creating cells that have only the necessary metabolic pathways).

Over time, synthetic-biology-based processes are expected to penetrate the chemical market, due to the advantages and continuing progress in performance as described above. Key chemical markets that are being targeted with synthetic biology include the more value-added applications, including fine chemicals (e.g., food and fragrance ingredients). In particular, these chemical products are suitable for smaller batch sizes and can be sold for higher prices, making them attractive markets for synthetic-biology companies.

For example, Evolva, a leading synthetic-biology company, is close to launching a natural stevia sweetener, EverSweet, which has a superior taste compared with existing stevia formulation. In particular, EverSweet does not have a bitter aftertaste, which otherwise prevents use of traditional stevia at higher concentrations.

The market size and forecast growth rate for synthetic-biology-enabled chemicals, by product type, is shown in the table below.

TABLE 89

GLOBAL VALUE OF ENABLED CHEMICALS MARKET, BY PRODUCT TYPE, THROUGH 2021
($ MILLIONS)

Product Type	2015	2016	2021	CAGR% 2016–2021
Polymers	749.7	818.9	2,078.8	20.5
Cosmetics	109.3	112.7	181.9	10.0
Enzymes	55.9	56.0	112.1	14.9
Surfactants	27.7	28.1	83.1	24.2
Lubricants	23.1	23.4	69.3	24.3
Flavors and fragrances	6.2	7.4	517.4	133.8
Other	175.8	203.8	287.3	7.1
Total	1,147.7	1,250.3	3,329.9	21.6

Source: BCC Research

The global value of synthetic-biology-enabled chemical products was over $1.2 billion in 2016 and is forecast to grow at an annual rate of 21.6% to reach a market size of over $3.3 billion by 2021.

BCC Research believes that synthetic-biology approaches to producing industrial chemicals will become more popular due to increasing pressure on companies to reduce their carbon footprint and to increase the sustainability of their operations. In addition, the main products that will come on the market in the next five years are considered “drop-in” as they can use existing industry infrastructure.

Many of the companies commercializing products are partnering to bring together diverse technologies and sets of skills.

A key factor for successful commercialization is the qualification of the new chemical to yield downstream products (e.g., polymers, fibers, textiles, etc.) that perform as well or better than with the conventionally produced chemical.

Several high-growth sectors within the chemicals synthetic-biology industry include flavors and fragrances, lubricants and surfactants.

The flavors and fragrances segment was valued at $7.4 million in 2016 and is growing at a CAGR of 133.8% to reach a forecast value of $517.4 million by 2021. Evolva has launched several products, including resveratrol (dietary supplement), vanillin (food flavoring), nootkatone (fragrance/insect repellent) and valencene (fragrance).

Flavors and fragrances produced by synthetic-biology methods have the potential to compete with those derived from natural plants, as illustrated by Evolva’s product portfolio.

Resveratrol has a range of potential health benefits (e.g., longevity and weight control) and is found in various plants, such as red grape skins.

Nootkatone is a flavor/fragrance that is derived from grapefruit or produced chemically from valencene. Evolva's ability to produce synthetic nootkatone should open up a potential market larger than the current market for naturally produced nootkatone.

Valencene is a flavor/fragrance traditionally derived from oranges. The chemical structure is similar to nootkatone.

Vanillin, marketed as Always Vanilla, is targeted at the high end of the vanillin market and as a natural vanilla flavor. Evolva's production methods enable low costs for this natural vanilla product.

Evolva's EverSweet stevia sweetner is scheduled to launch in 2018.

The polymers market segment is valued at $818.9 million in 2016 and is growing at a CAGR of 20.5% to reach a forecast value of nearly $2.1 billion by 2021.

A key polymer product is PDO, which is manufactured by DuPont using a synthetic-biology-enabled bioprocess as an intermediate for its Sorona polymer.

The PDO market is considerably larger than the DuPont Tate & Lyle plant, which produces 100 million pounds per year. PDO is used to make polytrimethylene terephthalate (PTT). PTT is a replacement chemical for polyethylene terephthalate and nylon, which have a wide range of applications. The PDO produced by DuPont is used to make Susterra, which is used in de-icing fluids, antifreeze and heat-transfer fluids. It is also used to make DuPont's Sorona polymer and Ceranol polyols. These products have broad markets. The main competitive process to making PDO is petroleum based.

Helping to drive the growth of the PDO market is the increasing consumption of PTT and polyurethane in various end-use industries.

Besides its present use in polymers, bio-PDO has a range of potential applications in composites, adhesives, laminates solvents and antifreeze agents, providing significant upside growth potential.

Polymer chemicals besides PDO that will be important in the forecast period include acrylic acid, propane diol, 1,4-butanediol (BDO), adipic acid, isoprene and farnesene. End-use markets that are attractive are those where packaging is a small proportion of the overall cost of the product.

The global market for BDO is 2.8 billion pounds per year, worth an estimated $4 billion. The product is currently manufactured by industry as a multistep process using petroleum-derived feedstocks including acetylene, propylene oxide and butadiene. BDO is used to produce solvents, fine chemicals and high-performance polymers (spandex fibers, engineered plastics, protective casings and soles of running shoes).

Genomatica and its partner Tate & Lyle are producing approximately 140 million pounds of BDO per year using dextrose sugars as a feedstock.

In addition, Genomatica's fermentation technology for producing bio-BDO is being commercialized by Novamont (30,000 tonnes per year plant in Adria, Italy) and BASF (75,000 tonnes per year plant).

Chemicals used to make polymers for tires are an important market for the synthetic-biology industry. In particular, snow tires require higher percentages of diene rubbers (e.g., butadiene), which improve their low-temperature properties.

One of the tire precursors, butadiene, is an important C4 chemical, and has a market size of more than 20 billion pounds per year. In addition to making rubber for tires, butadiene is used for electrical applications, footwear, plastics, asphalt modifiers, additives for lubricating oil, pipes, building components and latex.

The global supply of butadiene is decreasing due to a shift to natural gas by petrochemical cracking plants, and a lack of dedicated, butadiene-specific, production processes and plants.

Several synthetic-biology companies and partnerships are targeting butadiene as a product, including Genomatica and Versalis, LanzaTech and Global Bioenergies, Genomatica and Braskem, and Genomatica and BASF.

In February 2016, Versalis announced that it would be operating a demonstration-scale plant for making butadiene based on the Genomatica synthetic-biology technology. The butadiene is then used to produce polybutadiene (rubber).

In addition to these chemicals, specialty oils are used to soften the polymers, so that the tires can be used on the road. TerraVia is developing oils for this purpose.

Another chemical family used in polymers is polyhydroxy alkanoates (PHAs). PHAs are a family of biopolyesters that can be used in bioplastics. However, better PHA production strains need to be developed with lower production costs in order to compete successfully in this space.

The cosmetics market segment was valued at $112.7 million in 2016 and is growing at a CAGR of 10.0% to reach a forecast value of $181.9 million by 2021.

Allylix is currently selling two products in the perfume and cosmetic industry, nootkatone and valencene, which give an aroma of grapefruit and oranges, respectively. Allylix uses a proprietary synthetic-biology platform to engineer yeasts for producing these very pure terpene specialty chemicals.

In March 2011, TerraVia (then Solazyme) launched its Algenist anti-aging skin-care brand, targeting the luxury skin-care market and using Sephora SA as a marketing and distribution partner. The Algenist product uses alguronic acid, produced through synthetic biology from microalgae.

Amyris has developed a way to produce squalane via yeast-produced farnesene. Squalane is a high-quality moisturizer with applications in cosmetics, as an ingredient in skin-care lotions, hair-care creams, hand washes and lipsticks. Squalane is mostly produced from shark liver oil; however, this is expensive, time consuming and not environmentally friendly. The other natural source of squalane is ultrarefined olive oil. Because of the supply uncertainty and difficulty, manufacturers have reduced their use of the product during the past 10 years; as a result, the global market has gone from 7,500 tonnes per year in 2003 to 3,000 tonnes per year in 2015.

In our forecasts, BCC Research assumes that Amyris can expand the market for squalane from 3,000 tons per year to approximately 8,000 tons per year, and capture 3,500 tons of that expanded market. At a squalane price of $37,100 per ton, this means a market for synthetic-biology-produced squalane of $129.8 million by 2021.

BCC Research believes that this scenario is very reasonable, as Amyris already has a 20% market share and is supplying its product to more than 300 unique brands. The ability to create new market share is enhanced because synthetic-biology-produced squalane avoids any killing of sharks and provides a stable, steady supply of this valuable oil, thus attracting more brands.

Surfactants and lubricants include oils produced by Amyris as derivatives of synthetically produced farnesene.

Other chemicals include the important building block chemical, succinic acid. Succinic acid is used in de-icers, coolants, plasticizers and fuel additives. It is also the starting chemical for making BDO (used in copolyester ethers, polyurethanes and spandex fibers), gamma-butyrolactone (used for fine and specialty chemicals and pyrrolidones) and tetrahydrofuran (used as a common organic solvent).

Several biosuccinic acid plants are operating. Reverdia (a joint venture between DSM and Roquette Freres) operates a 10,000 tons per year plant in Cassano Spinola, Italy. BioAmber operates a 30,000 tonnes per year biosuccinic acid plant. Myriant’s biosuccinic plant in Lake Providence, La., has a capacity of 14,000 tons per year.

Enzymes include those for converting cellulosic feedstocks to simple sugars, which can be fermented to ethanol.

ENERGY MARKET

The energy market consists of biofuels including ethanol, diesel, jet fuel and butanol fuels. The global biofuels market is approximately $95 billion in size, of which synthetic biology makes up a very small portion today.

The main countries producing biofuels include the U.S., E.U. countries, China, Brazil and Argentina.

The main driving forces for advanced biofuel growth are shown in the table below, and include increasing concerns about the environment and fossil fuel dependence and government tax incentives and subsidies.

TABLE 90

ADVANCED BIOFUEL GROWTH FACTORS

Driving Force	Significance
Government regulations	Provide incentives and mandates for advanced biofuel companies, as well as drive market demand
Oil, gasoline and diesel prices	Declining prices make advanced biofuels less attractive and discourage investment dollars to the industry
Rising feedstock prices	Feedstocks influence the cost of production, and rising costs can reduce profit margins

Source: BCC Research

Overall, the market for biofuels is driven by government mandates, particularly blending mandates. More than 60 countries have blending mandates.

Key regulations include the U.S. Federal Renewable Fuel Standard Program (RFS2), the state of California Low Carbon Fuel Standard (LCFS) and the European Fuels Quality Directive.

The California LCFS requires that, by 2020, blenders, refineries, importers and distributors of transportation fuels reduce the carbon intensity of the fuels they sell by 10% below a 2006 baseline. Petroleum importers, refiners or wholesalers can either develop their own low-carbon fuel products or purchase credits from other companies that sell low-carbon fuels. Because California uses 18 billion gallons of transportation fuels annually, the LCFS standard will drive advanced biofuels consumption.

Transportation fuels are a strategic biofuels market segment for synthetic-biology companies. Transportation fuels are an important portion (greater than 75%) of today's global crude oil demand. Compared with transportation fuels, in the power generation fuels market there is stiffer competition for biofuels since several low-carbon renewable alternatives exist, including wind, solar and geothermal. Conversely, in the transportation market, biofuels are the only commercially viable low-carbon alternative to fossil fuels. This means that biofuels will continue to be promoted by the various regulatory agencies in the U.S. and Europe.

A key factor that has impacted the biofuels segment of the synthetic-biology industry is the decline in the price of crude oil during the five year period 2011 through 2016, shown in the table below.

TABLE 91

CRUDE OIL PRICES, 2011-2016

Date	Crude Oil Price ($/barrel)*
September 2011	82.48
September 2012	92.18

September 2013	102.36
September 2014	91.17
September 2015	45.06
September 2016	44.81

*Adjusted for inflation using the headline CPI.
CPI, consumer price index.

Source: BCC Research; www.macrotrends.net

Crude prices have dropped from a high in September 2012 of $102.36/barrel to $44.81/barrel in September 2016. Oil prices are not the only factor affecting the consumption of biofuels; other factors include national policies and political factors. Government mandates for bioethanol and biodiesel continue to play a role in market growth.

In addition to the drop in oil prices, the following factors are relevant: a decline in political will to fund biofuels projects after the 2008/2009 Great Recession; chronic overcapacity; and rising feedstock prices.

Newer technologies such as synthetic biology are affected by these factors. BP's decision in 2014 to exit the cellulosic ethanol business is an example of this phenomenon. BP had invested more than $750 million in this technology since 2008.

Countering these negative trends are government mandates, which will continue to play a role in the growth of synthetic biology for biofuels.

The recent macrofactors impacting the biofuels market have contributed to a shift in business focus for several synthetic-biology companies, as shown in the table below.

TABLE 92

STRATEGIC SHIFTS IN BIOFUELS

Company	Year	Strategic Shift
Codexis	2012	Refocus on pharmaceuticals
LS9	2013	Close business
Cobalt Technologies	2015	Close business
Solazyme (TerraVia)	2016	Refocus on specialty ingredients

Source: BCC Research

LS9 and Cobalt Technologies, both with a business plan focused on biofuels, closed their businesses in 2013 and 2015, respectively.

In 2012, Codexis terminated its biofuels alliance with Royal Dutch Shell and refocused its business on applications in pharmaceuticals. Likewise, Solazyme in 2016 refocused its business on specialty ingredients and changed its corporate name to TerraVia.

The table below shows the global value of enabled products in the energy industry, by product type.

TABLE 93

GLOBAL VALUE OF THE ENERGY MARKET, BY FUEL TYPE, THROUGH 2021
($ MILLIONS)

Fuel Type	2015	2016	2021	CAGR% 2016–2021
Ethanol	113.9	114.0	222.1	14.3
Diesel	72.5	73.1	151.5	15.7
Butanol	–	28.8	86.2	24.5
Other	–	0.7	130.0	–
Total	186.4	216.6	589.8	22.2

Source: BCC Research

The total market supplied by synthetic-biology-enabled advanced biofuel producers was valued at $216.6 million in 2016 and forecast to grow at a high CAGR of 22.2% to reach a market value of $589.8 million by 2021.

Since Europe has higher adoption rates of diesel engines, the primary market for renewable diesel produced with synthetic-biology platforms is expected to be in Germany, France and Italy.

The total market for synthetic-biology-derived biodiesel in 2021 is forecast to reach $151.5 million. The main synthetic-biology producing companies are expected to be Aemetis, Amyris and Joule Energy.

The E.U. produces approximately 60% of the world’s biodiesel, followed by the U.S. and Brazil. The major capacity expansions for renewable diesel in the next several years include North America (185 million gallons per year [MGY] capacity expected to be added through 2018) and France (200 MGY).

In August 2016, Amyris received a three-year contract from the U.S. Department of Energy covering the development of farnesene-based fuels. Amyris is working with Renmatix and Total New Energies USA to develop the manufacturing process to produce farnesene, a building-block chemical that can be used in diesel and jet fuels, among other applications.

The goal is for Amyris to produce cellulose-derived farnesene at a cost comparable with that of sugarcane-based farnesene. A production cost of less than $1 per liter would enable applications for this process in biofuels.

The U.S. ethanol industry is growing due to a strong market demand as well as federal and state financial incentives. A key legislative driver is the Renewable Fuel Standard (RFS), which sets goals for producing renewable fuels.

The two leading producers for ethanol are the U.S. and Brazil, accounting for more than 75% of world production. In the U.S., ethanol is produced mainly from corn, and in Brazil it is produced from sugar cane. The major capacity expansions for bioethanol in the next several years include North America (155 MGY capacity expected to be added through 2018), China (210 MGY), Brazil (47 MGY) and France (0.1 MGY).

The total market for synthetic-biology-enabled ethanol in 2021 is forecast to reach $222.1 million. The main synthetic-biology-producing companies are expected to be Aemetis, Algenol, BASF/Verenium, Beta Renewables, DSM/Poet, DuPont, Iogen and OPX Biotechnologies.

Butanol has several advantages over ethanol as a transportation fuel, notably the following: improved mileage; transport through existing gasoline pipelines due to butanol's immiscibility with water; and blending with gasoline in high proportions without any need to alter the existing internal combustion engine. Due to these advantages, and stated capacity goals of biobutanol producers, BCC Research forecasts significant demand for this product, reaching a market size of $86.2 billion in 2021. The main synthetic-biology producers include Gevo, Global Bioenergies and Green Biologics.

Other biofuels include jet fuel and other unspecified biofuels. The major capacity expansions for jet biofuel in the next several years include North America (240 MGY capacity expected to be added through 2018) and China (0.1 MGY). Brazil expects to add 20 MGY capacity in biocrude during the same time period.

AGRICULTURE MARKET

The table below shows the value of the agriculture market for synthetic-biology-enabled products. Synthetic biology can be used to produce more complex transgenic seeds, improve breeding in livestock and create novel pest-control strategies.

TABLE 94

GLOBAL VALUE OF AGRICULTURE MARKET, BY END USE, THROUGH 2021
($ MILLIONS)

End Use	2015	2016	2021	CAGR% 2016–2021
Animals	–	–	248.9	–
Pest control	5.5	7.1	137.5	80.9
Seeds	0.4	0.5	192.1	–
Total	5.9	7.6	578.5	137.8

Source: BCC Research

The agriculture market was valued at $7.6 million in 2016, and is growing at a CAGR of 137.8% to reach a market size of $578.5 million by 2021. The main market segments include animals, pest control and seeds.

Animals Market

The table below shows the global value of the animal market segment.

TABLE 95

GLOBAL VALUE OF ANIMAL MARKET, BY APPLICATION, THROUGH 2021
($ MILLIONS)

Application	2015	2016	2021	CAGR% 2016–2021
Beef feedlot	–	–	188.9	–
Dairy	–	–	32.3	–
Beef seedstock	–	–	27.7	–
Total	–	–	248.9	

Source: BCC Research

The synthetic-biology-enabled animal market is newly emerging and is expected to reach a value of $248.9 million by 2021.

The two main market segments for synthetic-biology-enabled animals include porcine and beef/dairy cattle. There are more than 1.2 billion pigs produced for slaughter each year, of which half are in China. Demand for genome-edited pigs is being driven by a shift in Asia from small-scale production facilities to larger, more integrated production that has a higher use of technology.

Genetically edited pigs have been produced that are resistant to porcine reproductive and respiratory syndrome (PRRS) virus. PRRS is caused by a virus and causes significant damage each year; for example, the disease costs U.S. producers more than $660 million annually. The CD163 protein allows the disease to spread, and pigs whose genes have been modified to prevent CD163 production do not contract PRRS.

Most beef cattle are bred in pasture by releasing bulls for natural breeding. Artificial insemination (AI) accounts for less than 10% of beef animals. However, competing demands for land and resources in this industry are driving the need for higher efficiency and thus toward AI and other genetic technologies such as in vitro fertilization, gender skew and genome editing.

In the dairy-cattle market, there is a large spread in milk yield among countries with similar AI levels. For example, Germany and China have similar adoption levels of AI, but Germany is nearly twice as high in milk yields compared with China. Thus, there is an opportunity to increase productivity by introducing elite genetics and other genetic technologies in these markets.

Pest-Control Market

The synthetic-biology market for pest-control applications was $7.1 million in 2016 and is growing at a CAGR of 80.9% to reach a forecast size of $137.5 million by 2021. The main market application in this period is for mosquito control.

Synthetic-biology methods for mosquito control compete with traditional technologies, as shown in the table below.

TABLE 96

MOSQUITO-CONTROL METHODS

Method	Advantages	Concerns
GMO mosquitoes	Can introduce market gene to monitor; high eradication levels (up to 90% population reduction); does not disturb other flying insects	Effect on indigenous population of mosquitoes; requires extensive safety and ecological impact testing
Irradiated sterile mosquitoes	Sterile insects are not self-replicating and cannot become established in the environment	Compete poorly for females; nonspecific genetic effects
Insecticide spraying to water, or bed nets, or indoors	Can be effective; targets species that breed in stagnant bodies of water; prevents mosquitoes from entering buildings; kills mosquitoes that land on walls	Low levels of eradication (10% to 40%); no monitoring possible; disturbance of other flying insects; strict controls to limit risk; development of immunity in mosquitoes; requires extensive safety testing
Reduce standing water sources	Can eliminate the need to use a pesticide; economical to implement	Manpower intensive; difficult to educate the general population; difficult to eliminate all standing pools in a given area
Larvicide treatment	Can help to reduce the adult population; can be applied to areas where mosquitoes breed	May miss some standing pools

GMO, genetically modified organism.

Source: BCC Research

A range of techniques are often employed, as no single method provides a 100% solution. The mix of methods can vary by municipality and country.

Insecticide spraying is very popular and works on mature mosquitoes that spread disease. Two classes of pesticides are approved in the U.S: organophosphates and pyrethroids. Organophosphates are very effective, but need strict controls on their use due to safety concerns. Pyrethroids are safer, but their widespread use has resulted in mosquitoes that are immune.

Synthetic-biology methods can produce novel approaches to controlling mosquitoes that spread diseases, and of agricultural pests that can harm crops. Key advantages of GMO mosquitoes is that this method is very effective at reducing the breeding population, can be monitored and does not disturb other flying insects in the area.

Initial attention has been focused on the *Aedes aegypti* mosquito, which can transmit several deadly diseases, including Zika virus, dengue and chikungunya. *A. aegypti* poses a serious public health hazard. The mosquito is present in more than 120 countries, and up to 40% of the world's population is exposed to infection as a result. There is a strong need to have effective control strategies for *A. aegypti*.

Ramp-up to peak sales for genetically modified insects in pest-control applications will be a slow process, taking up to 10 years in any given country. There are several reasons for this slow adoption curve. In any given jurisdiction, there are political considerations to releasing a GMO organism. Also, the best approach to handling outbreaks are still being developed and optimized.

The initial market will likely be local governments that will self-pay for the insect treatment programs. Additional market funding will come from grants from entities such as the Gates Foundation or World Health Organization (WHO) to service those areas that are unable to self-pay.

There are two initial markets for *A. aegypti* control, based on the 2016 Zika virus outbreak: Brazil and South Florida in the U.S, as shown in the table below.

TABLE 97

AEDES AEGYPTI INITIAL MARKETS

Feature	Brazil	Florida
Total spending on mosquito control	$1.2 billion	$100 million
Central/local split	50% central/ 50% local	100% local
Other features	Higher portion of budget is allocated to high infestation areas	Budget is growing at 15% annually, and a large share goes toward personnel costs

Source: BCC Research

Both Brazil and Florida have highly sophisticated mosquito-control programs. In Brazil, the overall spending for mosquito control is about $6 per person, with more funds diverted to high infestation areas. The central government funds about 50% of this effort, with the local municipalities funding the balance.

In Florida, the overall state mosquito control budget is more than $100 million and is growing at a high rate. Most of these funds are for personnel, versus chemicals. Chemicals are thought to be an inefficient way to control mosquitoes, being only able to kill 10% to 30% of insects in an infested area. The method preferred in Florida is to use people to drain places with standing water, and to use larvicides, which kill mosquito larva prior to their hatching.

Several synthetic-biology approaches are possible for the GMO mosquito market, including the traditional approach and gene-drive approaches. Oxitec is an example of the traditional synthetic-biology approach. Gene-drive approaches are thought to be further behind in development and commercialization because the modifications to the insect genome are passed onto future generations, and thus the impact on the overall ecology system is potentially greater and therefore will need to be studied more closely.

Oxitec's synthetic-biology-modified *A. aegypti* product, OX513A, is a leading candidate for use in the reduction or eradication of *A. aegypti* in affected regions. OX513A has undergone extensive testing and is scalable for manufacturing. Oxitec's facility in Brazil is able to produce 60 million male mosquitoes per week.

In early 2016, a Brazilian municipality, Piracicaba, tested Oxitec's OX513A GMO *A. aegypti* mosquito in a Zika crisis area that had approximately 5,000 people. The results of this field test showed an 82% reduction of *A. aegypti* in the infected area. The program was funded by the Piracicaba local government.

The Brazilian government has only given partial approval to OX513A, which means that municipalities use the product as an unlabeled product. Full approval requires specificity on how the product is used (i.e., who can use the insects and under what conditions). Questions that must be answered include what effect OX513A have on other mosquito species populations, to make sure that release of OX513A will not result in the spread of other infectious mosquito strains. In particular, there is concern about the Asian Tiger Mosquito, which transmits dengue and is a weaker vector.

In the U.S, the Food and Drug Administration (FDA) requires an Investigational New Animal Drug guidance, which has been filed, and then there is a period of answering questions which can take several years. Public comment is also required after the FDA releases a draft Environmental Assessment. The public commenting period can be quite long.

In the November 2016 U.S. elections, the voters in the Florida Keys voted in a nonbinding resolution to approve a measure allowing Oxitec to begin trial release of GMO mosquitoes to deal with the Zika outbreak. The FDA had earlier given its approval for the trial. As a result of the vote, the local Board of Commissioners approved the trials in the Keys area. If the trials go well, the next area would be in Miami.

Given these regulatory hurdles, the Brazil market followed by several Caribbean countries, the Cayman Islands and Panama are expected to be the first markets for OX513A.

The peak market potential for OX513A or similar insects is estimated to be $400 million, with ramp-up to this peak being influenced by critical outbreaks such as the Zika virus and the need for field trials and municipal and country approval processes. Longer term, the potential for increased funding from concerned agencies such as the Gates Foundation or WHO will increase the peak market potential for these products.

The initial mosquito vector for which synthetic-biology-enabled products will be sold is *A. aegypti*. Additional vectors include *Anopheles gambiae*, the most common carrier of malaria.

The market for GMO mosquitoes includes the self-pay and the large-grant market segments. The self-pay market includes local and regional municipalities that use public funds for insect control. The large-grant market includes stakeholders such as the Gates Foundation or WHO that have an interest in eradicating mosquito-born diseases.

The peak self-pay market is estimated to be $300 million. This includes the southern U.S, Brazil and the Caribbean.

The peak large-grant market is more difficult to estimate but is approximately equal to the self-pay market, or $250 million. This includes regions where public funding is not feasible such as Africa and Southeast Asia. As an example of this market, the Gates Foundation invested $75 million in the Target Malaria project, which is focused on training laboratory staff in how to obtain regulatory approvals and conduct field trials in Burkina Faso, Mali and Uganda.

The total peak market for GMO mosquitoes is thus estimated at approximately $550 million, with ramp-up predicted to be up to 10 years. Factors affecting the ramp-up rate include: the occurrence of significant outbreaks such as the recent Zika outbreak; the speed at which the field trials demonstrate effective insect control; how fast the GMO insect products can move through the local regulation channels; and general public sentiment surrounding GMO insects.

Seeds Market

The global market for synthetic-biology-enabled seeds is shown in the table below.

TABLE 98

GLOBAL VALUE OF SEED MARKETS, BY END-USE APPLICATION, THROUGH 2021 ($ MILLIONS)

End-Use Application	2015	2016	2021	CAGR% 2016–2021
Soybean	–	–	97.1	–
Canola	0.4	0.5	35.5	–
Cotton	–	–	24.6	–
Other	–	–	34.9	–
Total	0.4	0.5	192.1	–

Source: BCC Research

The synthetic-biology market for genome-edited seeds was $500,000 in 2016 and is forecast to reach a size of $192.1 million by 2021. The main application areas include canola, cotton and soybean.

Genetic engineering is essential to today’s biotech, or transgenic, seed industry. Genetic engineering is used to introduce one or a few foreign genes into a plant’s genome, to produce a desirable trait. These crops, called genetically modified crops, have existed for

more than 15 years and have achieved significant penetration in both the developed and developing countries.

Synthetic biology, using new genome-editing tools, offers a revolutionary new opportunity for modifying a plant's genome. Using these tools, a scientist can introduce new traits without randomly inserting bacteria-derived (i.e., foreign) genes. This opens up the possibility of non-GMO seeds that do not require regulatory oversight. In addition to a faster regulatory pathway, the new tools offer precision, specificity and speed for modifying the genome.

For crop plants, there are several key applications where synthetic biology is used for new seed products: resistance traits, stacked traits (i.e., insertion of several traits into one seed), and desirable traits.

The one seed product on the market in 2016 was a herbicide-resistant canola seed product, SU Canola. In the future, it is expected that synthetic-biology-enabled stacked trait and desirable trait seeds will also come onto the market. For example, Dow AgroScience's next generation of Smartstax products (multigene traits) will use genome-editing technologies.

The advantages of genome-edited crops, which are helping to drive the growth in this market, are shown in the table below.

TABLE 99

ADVANTAGES OF GENOME EDITING FOR CROP MODIFICATION

Advantage	Benefit
High specificity	Fewer off-target effects
Regulatory oversight	Fewer regulatory barriers
Rapid market introduction	Less regulation means faster commercialization
Enabling technology	Useful for identifying new gene functions
Facilitates gene stacking	Multiple new genes enable better crop performance
Market penetration	Enables wider market penetration to low-profit and/or small high-value crops
Greater range of traits	Novel gene functions can be introduced into a crop
Provides entry into non-GM markets	Allows for wider adoption of genome-edited crops in some European countries

GM, genetically modified.

Source: BCC Research

There are significant advantages and benefits of genome-edited crops, as shown in the table above. Higher specificity means that a single locus (e.g., 18 bp) within a large genome (e.g., up to 17 billion bp) can be targeted, reducing or eliminating any off-target effects.

In the U.S., if no foreign DNA is introduced, the product is not regulated. This means that genome-edited crops can be introduced into the market much more rapidly than if they were regulated. Should the FDA need to review any new genes introduced in the crop's genome, the process would be faster because the high specificity reduces any need to evaluate many thousands of insertion occurrences.

Genome editing can be used in agbio research to identify new gene functions by introducing gene knock-outs, deletions or alterations. This is important in plant research because a large percentage of genes in plants have an unknown function or are inactive.

Genome editing allows for insertion of multiple stacked genes or multiple genes on separate chromosomes. This opens up many possibilities for improved crop performance, particularly where the desired trait requires the function of many genes acting in a pathway. An example of this is the soybean, which requires multiple genes for nitrogen fixation.

Genome editing can also be applied to low-profit crops, such as wheat, and to smaller high-value crops such as vegetables. Novel gene functions can be altered to increase crop value. Such functions include allergen production (e.g., gluten), antioxidant levels (e.g., carotenoids) and enzymes responsible for fruit discoloration. These advantages of genome editing thus can open up new market areas for higher value crops.

Finally, genome editing, due to its non-GMO nature, may be considered more favorably by some countries in Europe, accelerating the adoption of this technique.

The table below gives the prospective market landscape for genome-edited crops for the forecast period.

TABLE 100

GENOME-EDITED CROPS MARKET LANDSCAPE
(MILLION TONNES)

Crop	Trait	Market Size (Million Tonnes)	Company
Soybean	Reduced trans fat; low lineoleic; nematode resistance; herbicide resistance	45	Calyxt
Potato	Better cold storage, and reduced actylamide levels	325	Calyxt
Canola	Reduced fat canola oil; disease resistance	65	Calyxt
Wheat	Reduced gluten levels; disease resistance	680	Calyxt

Source: BCC Research

The improvements in the table represent strong market needs that, if met by synthetic-biology tools, will drive market growth over the next five years. For example, a no-trans-fat soybean is in field trials by Calyxt and scheduled for product launch in 2018.

The crops listed in the table are major crops of high import to the world, and the traits introduced by synthetic-biology methods will give significant improvements to these crops.

Genome-edited traits can add high value to the price of agricultural commodities.

For example, improved soybeans that can produce oil that has higher oleic acid and lower linoleic acid content will reduce the need for hydrogenation (for heat stability and shelf life) and the creation of trans fats. The resulting oil is lower in saturated fatty acids compared with traditional soybean oil, and is more similar to olive oil.

The economic value that is available for such an enhanced soybean oil can be assessed by comparing the price of commodity soybean oil with that of olive oil. The commodity price for soybean oil in September 2016 was $829 per tonne and for olive oil was $3,980 per tonne for the same month. Some portion of this price difference could be captured by an engineered, enhanced soybean oil.

Similarly, enhanced traits in potatoes, canola and wheat can drive market values in these products.

Potatoes can be improved by blocking an enzyme that degrades sugars in the underground stem of the potato. Blocking the enzyme slows the sweetening of cold-stored potatoes (i.e., starch conversion to reducing sugars) and stops the generation of harmful acrylamide during frying.

In canola, the level of saturated fatty acids can be reduced by blocking an enzyme responsible for their synthesis. This results in lower saturated fat canola oil.

In wheat, some components of gluten cause an adverse immune system reaction, including inflammation of the small intestine. Genome editing can help to reduce these gluten chemicals in the wheat.

The commercialization pathway for agricultural product candidates is shown in the table below.

TABLE 101

GENOME-EDITED CROPS COMMERCIALIZATION PATHWAY

Stage	Description	Time
Initial research	Select crop, trait(s) and genetic modification strategy	1 to 2 years
Proof of concept	Do targeted mutations occur, and do they result in desired phenotype?	3 to 6 months
Field trials	When planted in fields, do mutated varieties produce desired phenotype?	1 year
Transfer to elite varieties	Implement desired mutations into elite varieties	3 to 6 months
Proof of concept – commercial	Field trials using the elite varieties	1 year
Grow commercial quantities	Sufficient quantities for commercial markets	3 to 4 years

Source: BCC Research

The commercialization steps involve initial research, proof of concept and field trials. If successful, this is followed by incorporating the genetic changes into high yield, commercial “elite” varieties (done by crossing multiple times) and showing proof of concept with additional field trials of the mutated elite variety.

Upon completion of these field trials, the seeds are ready to bring to market. It will take from three years to four years to grow sufficient quantities for commercialization. The overall development and commercialization process can range from 6.5 years to 9 years. This compares with traditional agricultural biotech genetically modified trait development times of approximately 13 years to develop and commercialize a product.

REGIONAL MARKETS

SYNTHETIC-BIOLOGY PRODUCTS BY REGION

The table below shows the global value of the total synthetic-biology market by region.

TABLE 102

GLOBAL VALUE OF SYNTHETIC-BIOLOGY MARKET, BY REGION, THROUGH 2021 ($ MILLIONS)

Region	2015	2016	2021	CAGR% 2016–2021
North America	1,830.6	2,050.1	5,326.6	21.0
Europe	818.6	894.2	3,016.5	27.5
Asia-Pacific	759.9	805.5	2,611.4	26.5
ROW	139.2	148.3	455.5	25.2
Total	3,548.3	3,898.1	11,410.0	24.0

ROW, rest of the world.

Source: BCC Research

Geographically, the synthetic-biology market was dominated by North America and Europe, with 52.6% and 22.9%, respectively, of the total market in 2016. Asia-Pacific was also a very important market, with 20.7% of the total 2016 market. “ROW” includes countries that are strategically important for biofuels and agriculture (e.g., Brazil and Argentina).

North America will continue to lead in synthetic-biology markets through 2021, given its strengths in life science infrastructure and public funding.

In pharmaceuticals, the main enabled products include antibiotics, diabetes and malaria drugs and influenza vaccines. These products have strong markets in Europe and Asia as well as North America.

In biofuels, Europe is a strong market, and Asia (China) and South America (Brazil) are important regions for ethanol.

Biologic components and enabling products closely track the genomic and proteomic geographical markets, with significant demand in both the North American and European regions.

North America (principally the U.S. but also Canada) plays a key role in synthetic- biology markets in several respects.

First, the region is a major consumer of genomics and proteomics tools and, as a result, of biologic parts and enabling products.

Second, North America provides significant end-user demand for synthetic-biology-produced products in the pharmaceuticals, energy, chemicals and agriculture industries.

Third, many of the synthetic-biology tools companies that are developing enabling technologies are located in this region. These include: Illumina and Thermo Fisher Scientific (DNA sequencing); Gen9, ATUM, Integrated DNA Technologies and Twixt (DNA synthesis); Cellectis, Cibus, CRISPR Therapeutics, Editas Medicine and Sangamo Therapeutics (genome editing); and Ginkgo Bioworks and Zymergen (integrated systems).

ENABLING PRODUCTS MARKET BY REGION

The table below breaks out the enabling products market, by geographic region.

TABLE 103

GLOBAL VALUE OF ENABLING PRODUCTS MARKET, BY REGION, THROUGH 2021 ($ MILLIONS)

Region	2015	2016	2021	CAGR% 2016–2021
North America	456.9	526.6	1,121.9	16.3
Europe	164.1	184.7	516.9	22.9
Asia-Pacific	63.7	66.8	239.3	29.1
ROW	7.6	7.9	36.4	35.7
Total	692.3	786.0	1,914.5	19.5

ROW, rest of the world.

Source: BCC Research

North America and Europe provide the bulk of the market demand for enabling products, comprising more than 90% of the $786.0 million market in 2016.

North America and Europe possess mature life science R&D infrastructure and talent, which allow these regions to dominate this market. In addition, these regions have strong support from government agencies for research in the main enabling technologies of genome editing, DNA sequencing and synthesis, and bioinformatics.

The Asia-Pacific region contains several countries that have advanced life science infrastructure, including Japan, China and South Korea. Growth in this region is forecast to be robust during the next five years based on strength in these countries.

CORE PRODUCTS BY REGION

The table below shows the synthetic biology core products market (i.e., biologic components and integrated systems) by geographical region.

TABLE 104

GLOBAL VALUE OF CORE PRODUCTS MARKET, BY REGION, THROUGH 2021 ($ MILLIONS)

Region	2015	2016	2021	CAGR% 2016–2021
North America	173.5	208.7	679.0	26.6
Europe	62.2	72.9	312.8	33.8
Asia-Pacific	23.9	26.8	144.9	40.1
ROW	2.9	3.1	22.0	48.0
Total	262.5	311.5	1,158.7	30.0

ROW, rest of the world.

Source: BCC Research

As is the case with enabling products, North America and Europe provided the bulk of the market demand for core products in 2016, comprising more than 90% of the $311.5 million market.

For 2021, BCC Research forecasts that these two regions, North America and Europe, will continue to make up the bulk of the forecast $1.1 billion core products market. The demand for core products in these regions is influenced by the same factors as for enabling technologies, primarily the status of the life science research and development infrastructure in those countries.

In addition, for core products, the presence in a country of a strong user base in the pharmaceutical, chemical, energy and agriculture industries can drive core product use.

ENABLED PRODUCTS BY REGION

The table below breaks out the enabled products market, by geographic region.

TABLE 105

GLOBAL VALUE OF ENABLED PRODUCTS MARKET, BY REGION, THROUGH 2021 ($ MILLIONS)

Region	2015	2016	2021	CAGR% 2016–2021
North America	1,200.2	1,314.8	3,525.7	21.8
Asia-Pacific	672.3	711.9	2,227.2	25.6
Europe	592.3	636.6	2,186.8	28.0
ROW	128.7	137.3	397.1	23.7
Total	2,593.5	2,800.6	8,336.8	24.4

ROW, rest of the world.

Source: BCC Research

North America, Europe and Asia provide the bulk of the market demand for enabled products.

Pharmaceutical, energy and chemical markets have strong demand in countries within Asia, particularly China.

The rapid industrialization of large Asian economies, particularly China and India, during the past twenty years has created demand for enabled products in the chemical, energy and agriculture markets. Many Asian countries have conditions that increase consumer demand for consuming products, including large populations, growing middle classes and a high proportion of younger people.

In the energy market, North America and China hold 57% and 24%, respectively, of the cellulosic ethanol installed capacity in 2015. They are followed by Brazil (9%) and the E.U. (9%).

The importance of region to the synthetic-biology industry is perhaps best illustrated in the energy market. Local-government incentives and mandates greatly influence the regional markets for biofuels. The future biofuels market in the geographic regions relies heavily on these mandates and financial incentives.

A common policy in the transportation fuel segment is the mandating of biofuel blending. More than 42 countries have mandates in place, covering bioethanol and/or biodiesel blends. In several key countries, the following blending mandates are in place, as described in the table below.

TABLE 106

BIOFUELS BLEND MANDATES IN KEY COUNTRIES
(%)

Country	Bioethanol (%)	Biodiesel (%)	Comment
Brazil	27.5	7.0	
Canada	5.0	2.0	Bioethanol can be up to 8.5% in various provinces.
China	10.0		In nine provinces
E.U.	5.8		
India	10.0	10.0	
Italy			0.6% advanced biofuels by 2018
Norway		3.5	
South Korea		3.5	
U.S.			Varies by state

Source: BCC Research

Brazil has a minimum ethanol content mandate of 27.5% and a biodiesel mandate of 7%. Legislation was signed into law on March 23, 2016, to increase the biodiesel mandate to 10% by 2019.

Canada has an RFS with 5% ethanol mandate and 2% renewable diesel. In addition, five provinces have individual mandates, with up to 8.5% ethanol.

In the U.S., the RFS program requires the Environmental Protection Agency to set annual volume requirements for four types of biofuels. The RFS requires 1.8 billion gallons of renewable fuel to be blended annually with transport fuel in 2016. This is up by 11% from 2014. By 2020, the requirement will be 36 billion gallons.

In addition to this federal standard, individual states have their own blending mandates. These mandates vary and can be up to 10% for ethanol (e.g., Hawaii, Missouri and Montana) and up to 5% biodiesel (e.g., Oregon and New Mexico).

The E.U. currently has a 5.8% first-generation ethanol mandate in place, and in September 2013, the European Parliament voted to put a cap of 6% of fuel demand by 2020. This is down from 10% originally mandated by the original Renewable Energy Directive.

Italy’s government decided in October 2015 to create a 0.6% advanced biofuels blending mandate by 2018. The intent is to put a policy in place to increase demand for next-generation fuels.

China has a 10% biofuels mandate to be reached by 2020, and nine Chinese provinces have mandated 10% ethanol blends, among which are Heilongjian, Jilin, Liaoning, Anhui and Henan.

India has a 10% ethanol and diesel mandate in place, and wants to move to a 20% goal for all biofuels by 2017.

Both India and China have growing automobile markets, and all new automobiles in India can run on 20% ethanol blends.

South Korea has a 2.5% biodiesel mandate, with a goal of increasing this to 3% by 2018. There is some opposition to this by the South Korean petroleum industry, claiming it will increase production costs.

Chapter 8

PATENTS

SYNTHETIC BIOLOGY: GLOBAL MARKETS

BIO066D
January 2017

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ISBN: 1-62296-433-0

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CHAPTER 8
PATENTS

INTRODUCTION

Synthetic biology is still a fairly new emerging technology. As such, the industry patent and intellectual property (IP) landscape is still developing and there are many issues to be determined in the future.

However, two trends are evident: a lack of consensus on foundational patents covering synthetic organisms, and a proliferation of patents on synthetic-biology parts and devices. In the field of synthetic organisms, no consensus seminal patents are blocking development. However, Synthetic Genomics' patents in this field may turn out to be seminal. The second trend, proliferation of patents on parts and devices, may create significant barriers in the industry.

A third issue is an ongoing debate over an open, versus proprietary, approach to synthetic-biology technologies. This creates conflicting interests. For example, gene-synthesis companies have significant proprietary positions, yet an open system of parts, devices and systems benefits these companies commercially. This is because widespread availability of these parts should increase demand for synthetic genes.

BioBricks (synthetic-biology components) are freely available on an open-source format. Since BioBricks are likely to be important components of an integrated system, synthetic organism or metabolic pathway, the intention is to make them available so patents on BioBricks do not block innovation in the industry. The corresponding model in the software industry is open-source software.

Patents covering synthetic biology have a wide scope, as shown in the table below. Patents can include biologic parts, metabolic pathways, genomes and integrated systems.

TABLE 107

SYNTHETIC-BIOLOGY PATENT SCOPE

Field	Definition	Patent Scope
Biologic parts	DNA and RNA part or gene and enzyme to perform specific function	Newly isolated or altered genes, enzymes or recombinant organisms containing them
Pathways	Several parts working together to perform overall process	Unique combinations of genes, enzymes or recombinant organisms. Methods for synthesizing existing products using these combinations
Genomes	Synthetic genomes	Genome design and synthesis, insertion into organism; synthetic organisms resulting from these methods

Integrated systems	Cellular systems to perform specific functions (e.g., produce chemicals and sensing)	Inserting synthetic-genetic cassettes into microorganisms for purposes of producing specific products; engineering cells to produce specific chemicals

Source: BCC Research

For biologic parts, important patents include novel genes, enzymes and the recombinant organisms that contain them. Pathways consist of genes, enzymes and recombinant organisms that function together to perform an overall process. Patents may include these combinations, as well as novel ways to synthesize products using these combinations.

Patents covering synthetic genomes include not only the sequence of the genomes themselves, but their design and synthesis, insertion into organisms and the resulting synthetic organisms.

Patents covering integrated systems include genetic cassettes used in microorganisms as well as engineered cells to produce specific chemicals.

FOUNDATIONAL PATENTS

Foundational patents are patents that claim fundamental ideas and either restrict freedom of movement in an industry or represent a fundamental concept.

Foundational patents in synthetic biology may be grouped into the following broad categories.

- Patents on fundamental ideas in synthetic biology (e.g., synthetic organisms, minimal genomes and biologic parts).
- Patents on fundamental biologic functions.
- Patents on classes of biomolecules with a particular function (e.g., nucleic acid binding proteins).
- Patents on synthetic genes or life forms.

The table below gives examples of several foundational synthetic-biology patents.

TABLE 108

SYNTHETIC-BIOLOGY FOUNDATIONAL PATENTS

Technology	Patent Number	Assignee
Systems and method for simulating operation of biochemical systems	US 5914891	Stanford University
Molecular computing elements, gates, flip-flops	US 6774222	U.S. Department of Health

Multistate genetic oscillators, bistable genetic toggle switches, adjustable threshold switch	US 6737269; US 6841376; US 6828140	Boston University
ZFPs	US 6903185; US 6610512; US 6607882	MIT, Scripps Institute, Sangamo Therapeutics
Minimal genomes	Glass, 2007	Synthetic Genomics
Minimal genomes	Blattner, 2006	Scarab Genomics
Synthetic genes	US 7262031	Verdezyne
Synthetic organisms	US2008/079299 (US application)	Synthetic Genomics

ZFP, zinc finger protein.

Source: BCC Research

The Stanford University patent claims that a fragment of DNA with a specific function that is combined with another part in a predefined way can define a biologic part. The patent may be very difficult to circumvent by others in the industry as it represents a fundamental idea about what constitutes a synthetic biologic part.

Patents on biologic functions that are used in many synthetic-biology applications may also be considered as fundamental. Examples include genetically encoded inverters (i.e., a device that takes an input signal and produces an inverted output signal encoded in DNA), gates, oscillators and toggle switches. Such patents have been issued to the U.S. Department of Health and Boston University.

Patents on classes of biologic molecules that have a particular function can also be considered as fundamental. For example, zinc finger proteins (ZFPs) bind specific sequences of DNA and can influence gene expression. Patents in this technology subclass are controlled (either owned or exclusively licensed) by Sangamo Therapeutics. It is possible that one could invent other technologies to circumvent these patents, but it would be difficult and costly. ZFPs can bind to every possible sequence of DNA and so any other technology solution may not be as desirable.

Key zinc finger patents include MIT (poly ZFPs with improved linkers), Scripps Research Institute (zinc finger binding domains for GNN) and Sangamo Therapeutics (regulation of endogenous gene expression in cells using ZFPs). Others have patented gene regulators using different technology, including Boston University (licensed by Cellicon Biotechnologies), which uses a dual RNA interference and repressor protein strategy. This strategy of workarounds using alternative technology solutions is a way to circumvent foundational patents.

Synthetic genes or life forms are also a source of foundational patents. Examples include minimal genomes and synthetic genes.

Synthetic Genomics and Scarab Genomics have obtained patents protecting technologies for creating minimal genomes in microorganisms. The Synthetic Genomics patent claims ownership of fewer than 400 genes required for sustaining a free-living microbe. The patent claims a synthetic genome can be inserted into a bacterium, which has its own genome removed, creating a chassis organism for synthetic biology. The patent also claims the use of this organism for the production of hydrogen or ethanol for fuel.

Synthetic Genomics' patent application (US2008/079229), covering synthetic organisms that are capable of translating proteins containing nonstandard amino acids, has important implications in synthetic biology. The technology, combined with the ability to synthesize whole genomes, allows for rewriting of the genetic code of existing or newly designed organisms.

The patents on artificial life forms are still too new to have been tested in the industry, and so we must wait to see how foundational they may eventually become.

Synthetic genes are the subject of foundational patents. Verdezyne owns a foundational patent relating to synthetic genes that was issued in 2007, entitled "Method for producing a synthetic gene or other DNA sequence" (US 7262031). The patent describes how to use a global (i.e., covering all possible correct and incorrect gene assemblies) optimization method for choosing a DNA code to make a protein. The patent is important because DNA fragments that are correctly used can enable the thermodynamically controlled self-assembly of only the desired DNA product. In addition to the gene assembly, its expression efficiency can be optimized using parameters also specified in the patent.

SYNTHETIC-BIOLOGY INDUSTRY PATENT ANALYSIS

An analysis of synthetic-biology-related patents by company and by technology subclass is provided in this section. The analysis excludes university patents, which are discussed in the foundational patents section above.

In the table below, the synthetic-biology industry can be grouped into four tiers, according to the number of patents issued or applied for by each company. Patents include both those applied for and those granted, and include all areas of the world.

TABLE 109

SYNTHETIC-BIOLOGY PATENT LANDSCAPE, BY COMPANY

Tier	Companies
Tier 1 (> 150 patents)	Ambrx, Amyris, BASF, Codexis, DuPont, Genomatica, Gevo, Integrated DNA, Intrexon, LanzaTech, Metabolix, MorphoSys, Sangamo Therapeutics, Synthetic Genomics and TerraVia
Tier 2 (50 to 150 patents)	Cellectis, Dow AgroSciences, Dyadic, Evolva, Gen9, Joule Unlimited, Life Technologies (GeneArt), LS9 and Sangamo Therapeutics
Tier 3 (10 to 50 patents)	Agrivida, Algenol Biofuels, Allylix, Beta Renewables, DuPont Pioneer, Editas, Ginkgo, OPX Biotechnologies (Cargill), Origene (Blue Heron), Precision BioSciences, Prokarium, Scarab Genomics and Verdezyne
Tier 4 (< 10 patents)	Arzeda, ATG Biosynthetics, Calysta Energy, Global Bioenergies, Sample6 and Synpromics

Source: BCC Research; FPO IP Research

The top tier group with more than 150 patents each includes Ambrx, Amyris, BASF, Codexis, DuPont, Genomatica, Gevo, Integrated DNA, Intrexon, LanzaTech, Metabolix,

MorphoSys, Sangamo Therapeutics, Synthetic Genomes and TerraVia.

These companies hold significant IP portfolios in key areas relating to synthetic biology and enjoy significant freedom of movement in developing and commercializing technologies in this industry. For example, Sloning BioTechnology (now part of MorphoSys) filed a U.S. patent (application US 20100022410) covering key technology for generating diverse protein libraries using synthetic DNA methods. This fits into Sloning's business strategy of using synthetic-biology methods in drug-discovery platforms.

A second tier of companies with between 50 and 150 patents includes Dyadic, Evolva, Gen9, Joule Unlimited, Life Technologies (GeneArt) and LS9.

These companies hold fewer overall patents but still have significant portfolios in key synthetic-biology areas. For example, LS9 has a strong patent portfolio covering the use of synthetic-biology-modified microorganisms that produce valuable end products.

The third tier of companies with between 10 and 50 patents includes Agrivida, Algenol Biofuels, Allylix, Beta Renewables, Ginkgo, OPX Biotechnologies (Cargill), Origene (Blue Heron), Prokarium, Scarab Genomics and Verdezyne.

These companies have a smaller patent portfolio, but usually have several key patents related directly to their business strategy. For example, Scarab Genomics holds foundational patents in minimal genomes, which is a core part of its synthetic biology business.

Finally, a fourth tier of companies have less than 10 patents. These companies include Arzeda, ATG Biosynthetics, Calysta, Global Bioenergies, Sample6 and Synpromics.

TABLE 110

PATENT DESCRIPTION BY COMPANY

Company	Snapshot Description
Agrivida	Transgenic plants with intein insertion sites in proteins that lead to switching phenotypes; plants that express specific proteins
Algenol Biofuels	Genetically enhanced cyanobacteria for production of ethanol; methods for producing these host cells; biofilm photobioreactor systems
Allylix	Production systems for isoprenoids; nootkatone applications in insecticides
Ambrx	Polypeptides containing nonnatural amino acids and methods of making such nonnatural amino acids
Amyris	Fuel compositions containing isoprenoid compounds; jet fuel compositions and methods to make; artemisinin production methods; isoprenoids
ATG Biosynthetics	Methods for generating RNA and poly-peptide libraries and their use
BASF	Genetic engineering of plants; transgenic plants; bacteria-producing S-containing chemicals; incorporation of genes from starch pathways into plants

Beta Renewables	Methods for recovering sugars from ligno-cellulosic biomass; pretreatment methods for ligno-cellulosic biomass
Blue Heron and Origene	Improving sequence fidelity; solid-phase polynucleotide production; removing errors
Calysta	C-1 metabolizing organisms for producing biofuels
Codexis	Enzymes and genes that encode enzymes
DuPont	Polynucleotides encoding for proteins relating to plants or pesticidal activity; biologic production of PDO; transgenic silkworm producing silk
Dyadic	Enzymes derived from fungi; improved cellulase enzymes; screening of expressed DNA libraries in filimentous fungi; methods for degrading lignocellulosic materials
Evolva	Cellular production systems for producing specialty chemicals, antibiotics, PPAR modulators; combinatorial gene-expression libraries
Gen9	Methods for in situ, microarray and microfluidic-based nucleic acid synthesis; high-fidelity assembly of nucleic acids; preparative in vitro cloning methods
GeneArt and Life Technologies	PCR, molecular-biology, sequencing; gene-assembly technologies
Genomatica	Multicellular in silico metabolic models; methods for biosynthesis of BDO, polypropylene, ADA, olefins, isopropanol and isobutanol
Gevo	Engineered microorganisms for increased yield in biotransformation of carbon sources into n-butanol and isopropanol
Ginkgo	Metabolic engineering methods to improve yields in cells
Global Bioenergies	Bioproduction processes for alkenes and isoprenol
Integrated DNA	DNA amplification, manipulation and labeling methods
Intrexon	Methods covering a range of gene-expression control and modulation technologies
Joule	Technologies to create light-harvesting and hyperphotosynthetic microorganisms to produce products for the energy industry
LanzaTech	Production of chemicals using microbial fermentation
LS9	Genetically modified microorganisms that consume renewable feedstocks; fatty acid biosynthetic pathways; producing low-molecular-weight hydrocarbons from renewable resources
Metabolix	Metabolic engineering; enzymatic biopolymer production; biologic systems for manufacture of polymers; biopolymer compositions; applications of PHA polymers; polymer extraction methods; medical and in vivo applications of polymers; chemically inducible expression of biosynthetic pathways; multigene-expression constructs
MorphoSys	Synthetic-biology methods for antibody discovery
OPX Biotechnologies (Cargill)	Metabolic pathway engineering
Oxitec (Intrexon)	Gene-expression systems for insect pest control
Prokarium	Synthetic-biology methods for engineering immune-cell-targeting bacteria that express vaccines from within the human body
Sample6	Synthetic-biology methods for modifying bacteriophage genomes and use of such systems for on-site environment monitoring

Sangamo Therapeutics	ZFP technologies
Scarab	Massively engineering microorganisms; minimal *Escherichia coli* genomes
TerraVia	Methods for evolving hydrogenase genes; production of tailored oils in heterotrophic microorganisms; light utilization in photosynthetic microorganisms
Synpromics	Design and construction of specific promoters for selective gene expression
Synthetic Genomics	Methods of genome installation in recipient host cells; seminal patents on synthetic life forms
Verdezyne	Engineered microorganisms

ADA, adipic acid; BDO, 1,4-butanediol; PCR, polymerase chain reaction; PDO, 1,30-propanediol; PHA, polyhydroxy alkanoate; PPAR, peroxisome-proliferator activate receptors; ZFP, zinc finger protein.

Source: BCC Research

The summaries in the table illustrate three types of strategies practiced in the industry: specialize in one technology subclass; integrate across several subclasses; or focus on industry foundational technologies.

Companies in the top two tiers tend to specialize in one technology subclass; for example, Sangamo Therapeutics specializes in integrated systems, Gevo, Amyris, LS9, TerraVia and DuPont specialize in enabled products and Life Technologies/GeneArt and Integrated DNA specialize in enabling.

Each of these companies has focused strategically on specific technology areas and built a substantial IP portfolio in that area. Other companies seeking to enter the industry must be aware of the IP portfolio of these companies and seek either licenses or ways to work around specific technologies, which may or may not be as effective.

In contrast to these strategies, other top-tier companies hold patents across multiple subclasses of synthetic-biology technologies. Examples of companies following this strategy include Synthetic Genomics and Amyris.

Several companies, including Metabolix, spread their patents across several synthetic-biology technologies. The strategy involves a broader participation in synthetic-biology technologies and capture of the value chain. It also requires a diverse set of core skills in order to commercialize patented technologies across a wider range of the synthetic-biology value chain. Sometimes these broad skill sets are available in one company, but more often a company will need to have an active program of strategic alliances for out-licensing, codeveloping or joint ventures in order to capture more of the value within patented technologies.

The data make clear that broad participation across each technology subclass within synthetic biology is difficult to do. Most of the companies specialize in specific technologies or applications. In this industry, it seems that complete capture or participation in the full industry value chain, without strategic alliances, is rare.

A third strategy is to focus on technologies that create industry foundational IP and that limit the freedom of action of other companies. Examples of this strategy are Synthetic Genomics (synthetic life forms) or Sangamo Therapeutics (gene regulation using ZFPs).

GENOME EDITING - CRISPR/CAS9 PATENT LANDSCAPE

Of strong interest in the synthetic-biology field during the past several years is genome editing. There has been significant activity in this area in the technology and commercial areas. In this section, the patent landscape of genome editing is briefly reviewed and analyzed.

The main patent areas for genome editing can be captured in four key technology areas: MegaNuclease, zinc finger nucleases (ZFNs), transcription activator-like effector nuclease, and cluttered regularly interspaced short palindromic repeats (CRISPR). The main organizations that have had patents assigned to them during the past 10 years (i.e., 2006 through 2016) are shown in the table below.

The IP of CRISPR/Cas9 technologies is clustered among a handful of institutions and, by extension, their affiliated companies. This landscape is shown in the table below.

TABLE 111

GENOME-EDITING PATENT LEADERS

Company/Institution	Number of Assigned Patents, 2006-2016		
	5 to 15	16 to 45	46 to 90
Sangamo Therapeutics			X
Cellectis			X
Dow AgroSciences			X
DuPont/Pioneer		X	
Harvard College		X	
MIT		X	
University of California	X		
Recombinetics	X		
Broad Institute	X		
Thermo Fisher Scientific	X		
Editas Medicine	X		
ToolGen	X		
Precision BioSciences	X		
Agilent Technologies	X		

Source: BCC Research

The 14 companies/institutions in the table lead the field of genome editing in terms of the number of patent publications assigned to them. The top-tier leaders include Sangamo

Therapeutics, Cellectis and Dow AgroSciences. The next tier includes Du Pont Pioneer, Harvard and MIT.

CRISPR/Cas9 technologies are an important part of the genome-editing technology field, and this technology has gained much interest in the past few years. The table below summarizes the key academic institutions, their commercial affiliates, and current IP position with respect to CRISPR/Cas9 genome-editing technologies.

TABLE 112

CRISPR-CAS9 IP LANDSCAPE

Institution	IP Position	Commercial Spinout
MIT– Broad Institute	Was granted first CRISPR/Cas9 patents in December 2015, as a result of fast-track USPTO program	Editas
Harvard University–Broad Institute	Received several initial patents at the same time as the MIT–Broad Institute in 2015	Editas
University of California Berkeley/University of Vienna	Applied for patent coverage ahead of MIT/Harvard in 2015, but did not use the fast-track process. Has made Suggestion of Interference claims in courts	Intellia
University of Vilnius	Patents files in 2012, and cover Cas9 targeting DNA that is spaced three nucleotides from the PAM sequence	Dupont
The Rockefeller University	Research at Rockefeller showed CRISPR targeted DNA and could be used in gene editing. Rockfeller is listed on five of the Broad Institute patents	Intellia
Seoul National University /ToolGen Inc.	ToolGen, affiliated with Seoul National University, developed ZFN technology, which evolved into use of Cas9 nucleases. ToolGen also has developed a double-nicking method with ZFN to cleave the DNA. ToolGen has filed Suggestion of Interference claims covering two of its patents and five Broad Institute patents	Thermo Fisher Scientific

CRISPR, cluttered regularly interspaced short palindromic repeats; IP, intellectual property; PAM, protospacer adjacent motif; USPTO, U.S. Patent and Trademark Office; ZFN, zinc finger nuclease.

Source: BCC Research

The CRISPR/Cas9 patent field is complex, with multiple players having IP rights. The table above shows the fundamental importance of academic institutions in the development of the technology. It also demonstrates the academic–commercial interplay that is important to bringing a new technology to the market.

The Broad Institute, MIT and Harvard University performed early work in CRISPR-Cas9 through Dr. Feng Zhang (MIT) and Dr. George Church (Harvard University). Dr. Zhang subsequently founded the company Editas Therapeutics.

Dr. Jennifer Doudna (University of California, Berkeley) and Dr. Emmanuelle Charpentier (University of Vienna) made discoveries related to Cas9, including that the enzyme could cut DNA. Dr. Doudna was also an original founder of Editas and left that company to found Caribou Biosciences. Caribou Biosciences later cofounded Intellia Therapeutics. Dr. Charpentier is affiliated with CRISPR Therapeutics.

Dr. Virginijus Siksyns (University of Vilnius) performed work with Cas9 around the same time, showing that Cas9 could cut double-stranded DNA precisely three nucleotides away from the protospacer adjacent motif sequence. DuPont has rights to this technology in the agricultural field.

Dr. Luciano Marraffini (Rockefeller University) showed that CRISPR can target DNA and could be used in genome editing. Intellia Therapeutics secured the rights to this technology.

ToolGen, affiliated with Seoul National University, is involved in ZFN genome editing, with the use of Cas9 nucleases. ToolGen also uses a double nick approach with ZFN to cleave DNA, to reduce any off-target effects. Thermo Fisher Scientific has the rights to this technology.

Chapter 9

COMPANY PROFILES

SYNTHETIC BIOLOGY: GLOBAL MARKETS

BIO066D
January 2017

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ISBN: 1-62296-433-0

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CHAPTER 9
COMPANY PROFILES

20N LABS INC.

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20n Labs Inc., founded in 2013 as a spinout from the University of California, Berkeley, designs synthetic microbes using proprietary software.

The business model 20n is using is to elicit from a customer company the particular molecule they want to manufacture, and then design a microbe that can accomplish that. After doing this, 20n Labs then licenses the technology to the customer company.

ABEONA THERAPEUTICS INC.

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Abeona Therapeutics Inc., founded in 1989 under the name PlasmaTech Biopharmaceuticals, is developing gene therapies and gene-editing approaches for treating rare diseases. For gene editing, Abeona uses a cluttered regularly interspaced short palindromic repeats (CRISPR)/Cas9 platform. These therapies are directed at rare diseases and are in the research stage (preclinical).

The company's lead products are gene therapies for Sanfilippo syndrome (MPS IIIB and IIIA), juvenile Batten disease and Fanconi anemia (FA). The FA therapy is using the CRISPR/Cas9 gene-editing approach.

In addition to these therapies, Abeona markets MuGard, a mucoadhesive oral wound rinse for treating mucositis, stomatitis, aphthous ulcers and traumatic ulcers, and ProctiGard, a mucoadhesive oral wound rinse for treating rectal mucositis and radiation proctitis.

ACTIVE MOTIF

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Active Motif provides cell-biology-based research tools and informatic services to the life science research industry. The company offers a wide range of products, including synthetic-biology tools through its acquisition of SwitchGear Genomics in March 2013.

SwitchGear Genomics, founded in 2005 as a spinout from Stanford University, provides synthetic-biology tools that regulate gene expression and can be used to study regulatory elements in the human genome. SwitchGear's platform, called LightSwitch Luciferase Assay System, uses a unique synthetic gene that has very high brightness.

A key business objective of SwitchGear is to supply an end-to-end reporter assay system, so researchers can perform reporter assays rapidly with the need for cloning or reagent optimization.

AGILIS BIOTHERAPEUTICS LLC

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Agilis Biotherapeutics LLC is using synthetic-biology tools to develop DNA-based therapeutics for rare genetic diseases.

The lead program is for Friedreich's ataxia (FRDA), a neurodegenerative disease.

In December, 2013, the company formed an alliance with Intrexon to develop synthetic DNA-based therapeutics to repair or replace defective DNA in FRDA and produce the frataxin protein. The resulting drug candidate, which contains a unique gene construct developed with Intrexon, is AGIL-FA.

In August 2016, the U.S. Food and Drug Administration (FDA) granted Orphan Drug Designation to AGIL-FA, marking the first therapy for treating FA to receive this designation.

AGRIVIDA

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Agrivida, founded in 2003 as a spinout from MIT, is using synthetic-biology tools to develop feed crops for the production of biofuels and bioproducts from nonfood agricultural residues and biomass crops.

The table below contrasts Agrivida's technical approach with conventional methods of processing biomass into biofuels or chemicals. In the first step, Agrivida uses

synthetic-biology tools called GreenGenes, which involve inserting cell-wall-degrading enzymes into crops and residues that can be activated by protein switches by heat or a pH change. The enzymes break down the cell walls, allowing for production of fermentable sugars at low temperatures and pressures in the second step.

TABLE 113

AGRIVIDA TECHNICAL APPROACH

Process Step	Current Process	Agrivida Process
Obtain crops	Natural biomass crops and residues	Synthetic-biology-based crops and residues with cell-wall-degrading enzymes
Pretreatment	Milling at > 130°C	Milling at < 100°C
Saccharification and fermentation	Add enzymes	No enzymes added

Source: BCC Research

The key to the technology is the protein switch, called INzyme, which uses self-splicing peptides called “inteins.” In crops engineered with these switches, the enzyme is inactive during the crop’s growth stage. After the crop is harvested, these inteins can be removed by heat activation. This causes the proteins to change shape, become active and breakdown cellulose.

Compared with conventional treatment technology, the use of synthetic biology allows the biomass to be broken down with milder pretreatment and without incurring the cost of adding enzymes.

ALGENUITY

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Algenuity is developing and marketing algae-based technologies for the life science and synthetic-biology industries.

Algenuity provides its Algem photo-bioreactor for use in algae and cyanobacteria research. This is a laboratory-scale bioreactor. The company also provides Algenious services for modifying microalgae for synthetic-biology applications.

AMBRX INC.

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Ambrx Inc. is developing antibody protein drugs that use amino acids not found among the 20 used by most life on Earth. The company has advanced several antibody drug conjugate (ADC) programs through the preclinical stage.

ARX788 aHER2 ADC (oncology) is in Phase I clinical trials. Partnered programs include ARX618 FGF21 for diabetes (Bristol-Myers Squibb, in Phase II clinical trials), ARX720 Relaxin for heart failure (Bristol-Myers Squibb, Phase I) and Imrestor for mastitis in cattle (Eli Lilly, Phase II).

AMYRIS INC.

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Amyris, founded in 2004 as a spinout from the University of California, Berkeley, is developing and commercializing a synthetic-biology platform for producing specialty chemicals and transportation fuels. Amyris developed its Hi-Ryse (Hyper-integration for rapid yeast strain engineering) platform, which allows it to design, engineer, optimize and scale-up synthetic-biology-developed organisms for industrial fermentation. Hi-Ryse uses site-specific genome engineering and high-throughput multiplexing for screening. This reduces greatly the development cycle for moving a molecule from conception to commercial production.

Amyris uses Brazilian sugarcane as its primary feedstock, and has several joint ventures and alliances with Brazilian ethanol and sugar producers.

In September 2015, Amyris indicated that it would begin producing a new fragrance molecule, which had been developed using Hi-Ryse technology. This confirms Amyris' position as a leader in using synthetic biology in the flavors and fragrances market.

Amyris is developing as many as 17 molecules as part of industrial collaborations, using its Hi-Ryse platform.

In March 2016, Amyris announced that it would expand its Brazil industrial fermentation plant by adding a separate flavors and fragrances section. The new plant will produce farnesene as well as up to five high-performance fragrance molecules.

Amyris' Personal Care Business consists of flavors, fragrances, food ingredients and

cosmetic ingredients. This business unit accounted for $25 million in sales in 2015 and was a main contributer to Amyris' revenue growth in 2016.

The initial chemical and fuels products are based on the molecular building block, Biofene (trans-β-farnesene), which is produced via fermentation using genetically altered microbes.

ARAKNITEK

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Araknitek, founded as a spinout from Utah State University, is commercializing products made of synthetic spider silk proteins. The company is producing these proteins using transgenic Escherichia coli bacteria, silk worms and goats.

Applications for fibers made from these proteins include films, sprays, liquids, resins, fibers and fabrics.

ARZEDA CORP.

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Arzeda Corp., founded as a spinout from the University of Washington, is developing and marketing synthetic-biology-designed cell factories that are capable of industrial (specialty and bulk) chemical production.

The company uses proprietary technologies, including computational enzyme design, protein optimization and metabolic engineering, to develop these cell factory platforms.

The main synthetic-biology concept that Arzeda is developing is the computational de novo design of synthetic enzymes that have new properties and catalytic sites. This technology is complemented with existing synthetic-biology tools (e.g., large-scale DNA synthesis and computer-aided design [CAD] software) to design new biologic pathways and cell factories.

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AstraZeneca PLC, formed in 1999 as a result of a merger of Zeneca Group PLC and Astra AB, is one of the world's major pharmaceutical companies. Revenues are derived from cardiovascular drugs (34% of sales), neuroscience agents (14%), gastrointestinals (17%), oncology drugs (12%), respiratory products (16%) and other drugs and businesses (7%).

AstraZeneca has a high-growth pipeline, which is focused on immuno-oncology, oncology, respiratory, inflammation and cardio/metabolic applications. Immuno-oncology is a key focus for AstraZeneca and one where synthetic biology can have a significant impact.

AstraZeneca has four collaborations for using CRISPR genome-editing technology in its drug-discovery and development programs. These collaborations, started in 2015, include several institutions (Wellcome Trust Sanger Institute, the Innovative Genomics Initiative and the Broad Institute) and one company (Thermo Fisher Scientific).

ATG BIOSYNTHETICS GMBH

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ATG (Artificial and Technical Genetics) Biosynthetics GmbH manufactures and markets a range of synthetic-biology tools, including synthetic genes, synthetic oligonucleotides, gene cassettes, gene assemblies and clusters, artificial genetics software, protein-design tools and synthetic-biology consulting. The main impact of ATG's tools is to improve the function of gene products, including RNA, structural proteins, enzymes and small molecules. The main market for ATG's products is for protein expression.

The company's platform consists of a multiplex system for multiprotein expression with functional expression cassettes individually designed for co-expression.

The company also provides novel and artificial gene arrangements to achieve better protein function and activity.

ATG's PepID system generates bio-based peptide libraries. PepID separates hosting and expression into two subsystems, with peptides being produced in a biologic system (e.g., bacterial) from a plasmid DNA construct.

ATUM

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ATUM (formerly known as DNA2.0), founded in 2003, manufactures and markets synthetic DNA products.

ATUM is a leading provider of synthetic genes in the U.S. and globally. Key end-user markets for ATUM synthetic-gene products include biotechnology, large pharmaceuticals, chemicals and academia.

ATUM's GeneGPS Expression Optimization technology is a codon-optimization algorithm that gives high protein expression. This performance level gives ATUM a key advantage in this market.

Synthetic genes have key advantages over naturally produced cloned genes, including fast and low-cost synthesis; further, they are easily modified to optimize downstream manipulations, they have improved protein expression (from 10 to 100 times greater yields) and they have flexibility for any sequence.

The reason that synthetic genes can express more protein than a native gene is that native genes evolved for balanced expression of all genes within the cell and not for high expression of any single gene.

Cloning costs include purchase of oligonucleotides and molecular-biology kits, labor and sequencing. Purchasing synthetic genes is often much less expensive than cloning.

In March 2016, ATUM expanded into a 50,000 square foot facility in Newark, Calif. This expansion allows ATUM to integrate the production of both DNA and proteins into a single facility.

In April 2016, ATUM acquired MIGS LLC, a contract research organization specializing in producing antibodies and antibody-like molecules. This acquisition gives ATUM additional capabilities in antibody production and analysis technologies.

AVIDBIOTICS CORP.

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AvidBiotics Corp. is using synthetic-biology tools to develop therapeutic proteins that can selectively destroy target cells, including cancer and virus-infected and pathogenic bacterial cells.

The company has exclusive access to technology for generating families of phage that exhibit diverse tails that can bind to mutant bacterial forms. This library is useful for developing phages against bacteria that have mutated to change their sensitivities to antibiotics or surface receptors for phage.

AvidBiotics' technology platform uses a family of diversity-generating retro-elements (DGRs) that can create varied DNA sequences and thus proteins. DGRs are engineered

into phages to diversify the amino acid sequence of the receptor-binding site of the phage tail receptor. The result is a library of phages that may contain up to one trillion different tails targeting a pathogen's cell surface receptors.

BASF AG

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BASF AG is the world's leading chemicals company, and is global in scope with customers in over 170 countries and production sites in 41 countries. The five major business segments of the company are Chemicals, Performance Products, Functional Materials & Solutions, Agricultural Solutions and Oil & Gas.

The company is ahead of Dow Chemical, DuPont and Bayer in terms of its market share in the chemical products industry. As a leading chemicals company, BASF stands to improve its competitive position by adopting more efficient production biosynthesis tools such as synthetic biology.

BASF pursues a strategy of using the byproducts of one process as raw materials for a second process, called "integrated production." This achieves cost savings and synergies across business units including research and development (R&D) and purchasing. This strategy is also significant to BASF's pursuit and use of synthetic-biology technology. Synthetic biology enables bio-based feedstocks to be used as core raw materials for multiple products. This achieves significant cost savings across the company.

BASF is focusing on bio-based processes for its agrochemical (fungicides, herbicides and insecticides) and fine chemical (vitamins, carotenoids, amino acids, enzymes, nutraceuticals and pharmaceutical active ingredients) products.

The company is developing synthetic-biology tools to support its strategy for more bio-based processes. Besides its basic R&D, the company is working through its SunGene GmbH subsidiary, to develop new ways for precisely engineering plant genomes.

In May 2013, BASF formed an alliance with Genomatica, in which BASF will produce BDO (1,4-butanediol) from renewable feedstocks using Genomatica's synthetic-biology-based BDO process technology. BASF is the world's market leader in BDO production. Genomatica uses a modified E. coli fermentation process for its BDO process. The fermentation process uses dextrose as a renewable feedstock.

BASF plans to expand its production to several BDO derivatives based on renewable feedstock, including polytetrahydrofuran.

The alliance with Genomatica is strategic for BASF because it allows the company to ramp up bio-based chemicals including butadiene and butanediol in the future. With the price of

natural gas decreasing, there may be more natural gas sourced at the expense of less naphtha, making the demand for bio-based chemicals higher.

In September 2015, BASF extended its agreement with Genomatica, adding selected countries in Southeast Asia to the scope. BASF has rights to build a plant for up to 75,000 tons per year of BDO using Genomatica's Geno BDO process technology. This extension adds to the strength of the BDO business in the Asia-Pacific region.

In September 2013, BASF acquired Verenium Corp. (San Diego, Calif.). Verenium Corp., founded in 1992, is developing products in the biofuels and specialty enzyme markets using synthetic-biology platforms. The three main markets for the company's enzyme business include animal health and nutrition, grain processing and oil-seed processing.

Verenium is leveraging its technology platforms with an integrated value-chain strategy in the biofuels business. The company has developed capabilities in feedstock pretreatment, novel enzyme and microbe development, fermentation and process engineering. The enzyme and microorganism technologies allow flexibility on the front end of the value chain, allowing Verenium to produce ethanol from a wide variety of feedstocks including sugarcane bagasse, dedicated energy crops, agricultural waste and wood products.

The company operates two cellulosic ethanol pilot plants in the U.S. (Jennings, La., and San Diego, Calif.)

Verenium's R&D group has expertise in synthetic-biology tools, including gene discovery and optimization, cell engineering and microbiology. Verenium has a strong intellectual property (IP) position, with over 350 patents.

BAYER AG

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Bayer AG is one of the world's largest healthcare and chemical companies. The company has three primary business segments: HealthCare (52.7% of 2015 fourth quarter revenues), Covestro – formerly Material Science (25.5%), and Crop Science (21.8%).

The HealthCare division develops and markets products for preventing, diagnosing and treating diseases. Bayer CropScience, responsible for the agricultural business, is one of the world's leading crop science companies in seeds, crop protection and nonagricultural pest control.

Given the markets that Bayer covers, the company has an interest in synthetic biology and how it may help drive innovation and business.

In May 2013, Bayer HealthCare signed a three-year agreement with the University of California Institute and Mission Bay Capital (seed-stage funding company) covering the

evaluation, funding and initiation of startup companies. This partnership provides rapid access to new companies working on a number of technologies, including synthetic biology.

The Bayer Lifescience Center (BLSC), established in 2015, is a vehicle through which Bayer is pursuing synthetic-biology technologies, through partnerships with biotechnology companies. In 2015 and 2016, BLSC formed two relationships in genome editing to advance Bayer's drug-discovery and development platforms.

In December 2015, BLSC formed a joint venture with CRISPR Therapeutics covering the use of gene-editing technologies to discover and develop new therapeutics for blood disorders, blindness and congenital heart diseases. For applications beyond these three diseases, CRISPR Therapeutics will have rights for human use, while Bayer will have rights to nonhuman use, such as agriculture.

In May 2016, Bayer formed a partnership with ERS Genomics, giving Bayer access to ERS' CRISPR/Cas9 patents.

In both of these partnerships, Bayer will contribute its protein engineering and relevant disease know-how.

BETA RENEWABLES

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Beta Renewables, founded in 2011 as a joint venture between Biochemtex and Texas Pacific Group (U.S), is developing and commercializing synthetic-biology-based processes for biofuels and chemical intermediates.

The company's main platform is Proesa, a technology that allows the use of sugars in lignocellulosic biomass to obtain fuels and other chemicals.

BIOAMBER INC.

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BioAmber's technology platforms include industrial biotechnology and chemical catalysis. BioAmber is a leading supplier of bio-based succinic acid from renewable feedstock. Succinic acid is a key building-block chemical that can be used to produce a wide range of downstream chemicals.

BioAmber's yeast platform converts renewable sugars to succinic acid and BDO.

BioAmber began producing bio-based succinic acid in January 2010 at its 350,000-liter demonstration plant in France. The company now produces the bio-based chemicals of succinic acid, BDO and disodium succinate.

BioAmber's major strengths include owning a commercial-scale plant (France) and lower costs versus other succinic acid producers such as Gevo.

The company's new plant in Sarnia, Ontario (Canada), commissioned together with partner Mitsui in late 2015, has a capacity of 30,000 tonnes of biosuccinic acid per year. A distributor, Vinmar (Houston, Texas), has agreed to take up to 300,000 tons per year of biosuccinic as well as other bio-based chemicals produced by the plant in the future.

In June 2015, the Flokser Group, a producer of leather and suede fabrics, announced that it was launching an artificial leather fabric using bio-based materials supplied by DuPont Tate & Lyle Bio Products and BioAmber. The new fabric, launched under the Sertex brand, uses BioAmber's succinic acid and DuPont's Susterra 1,3-propanediol (PDO).

The global addressable market is 330 million pounds per year, 165 million pounds for biosuccinic acid, and 165 million pounds for bio-PDO.

BIO BASIC CANADA INC.

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BioBasic Canada Inc., founded in 1990, is a supplier of genomics products and services, including synthetic oligonucleotides and genes. BioBasic's commercial focus is on providing life science laboratories with biochemical products and services. Products include chemicals (e.g., buffers, stains, antibiotics and nucleotides), molecular-biology kits, polymerase chain reaction (PCR) products, vectors, culture medium and labware.

The company supplies both standardized genes and value-added genes. BioBasic is vertically integrated in the upstream gene-synthesis value chain. The company uses its own oligonucleotide manufacture as raw materials for its gene products. It also uses its dedicated DNA-sequencing facility for gene quality control.

BIOMAX INFORMATICS AG

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Biomax AG, founded in 1997, develops and markets software for the life sciences industry.

Biomax is partnered with DSM on SYNOP-X (Synthetic Biology Open Exchange), which facilitates open exchange of information among synthetic-biology companies and institutions. The platform includes a novel DNA parts registry and a CAD platform for DNA construct design.

Biomax offers its BioXM Knowledge Management Environment for use in synthetic-biology applications. This platform helps researchers to create complex pathways and DNA sequences, build and characterize parts repositories and use these repositories to design biologic systems that serve a function.

BIONEER CORP.

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Bioneer, founded in 1992, develops, manufactures and markets molecular diagnostic products, gene therapy drugs and genetic engineering research products. A key product area for research products is DNA synthesis, including synthetic genes and DNA constructs.

Bioneer is one of the world’s lowest-cost producers of oligonucleotides. Among gene-synthesis companies, Bioneer is fully integrated in the value chain as it produces the amidite building blocks as well as the oligonucleotides. This gives the company a cost advantage in this market segment.

Complementing its business in DNA synthesis, other products for the genomic tools markets include PCR equipment and reagents, as well as DNA and RNA extraction and amplification kits.

Besides its plants in South Korea, the company has a production plant in California and a sales and marketing office in the U.K.

BIO S&T INC.

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Bio S&T Inc., founded in 1996, supplies genomic research products and services, including services relating to DNA sequencing and gene synthesis. The company has approximately 15 employees. The company is focused on supplying genomics products and services to the Canadian market, including academia, biotechnology and big pharma companies.

BIO S&T is a second-tier gene-synthesis company, with a primary focus on molecular-biology products and services.

BLUEBIRD BIO

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bluebird bio Inc., founded in 1992 as Genetix Pharmaceuticals Inc., is developing gene therapies for severe genetic and rare diseases. The company's lead T-cell-based therapy is bb2121, which is in Phase I clinical trials for treating relapsed and refractory multiple myeloma. bluebird uses a transcription activator-like effector nuclease (TALEN) gene-editing platform for its T-cell therapies.

bluebird has collaborations with Celgene and Kite Pharma (to develop second-generation T-cell therapies against human papillomavirus [HPV] type 16 E6 oncoprotein).

BLUE MARBLE BIOMATERIALS

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Blue Marble Biomaterials, founded in 2005, is producing bioesters for the plastics, food flavoring, fragrance and adhesives industries.

Blue Marble's technology platform, AGATE (Acid, Gas and Ammonia Targeted Extraction), employs modified anaerobic fermentation, nongenetically modified organism (non-GMO) bacterial consortia to produce various chemicals. A key part of the platform is bacterial conjugation between different microbial strains that specialize in the breakdown of various

feedstocks. This provides flexibility for Blue Marble to handle a variety of feedstocks, including food waste, yard waste, spent brewery grain, algae, milfoil and corn silage, among others.

In January 2013, Blue Marble formed a distribution alliance with Sigma Aldrich (SAFC) in which Blue Marble's specialty chemicals will be sold under the SAFC portfolio.

In June 2016, Blue Marble launched its Natural Solutions flavors product line, with 14 unique esters. The flavors meet the definitions of "natural" labeling in the U.S. and Europe.

BOLT THREADS

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Emeryville, CA 94608
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Website: www.boltthreads.com

Bolt Threads Inc., founded in 2009, is focused on developing and marketing high-performance fibers. The company emulates the metabolic pathway developed by spiders for making silk to make synthetic fabrics. The technology works by inserting genes into yeasts, which in turn produce silk spider proteins.

In May 2016, Bolt Threads formed a partnership with Patagonia, covering the development of textile products incorporating Bolt Threads' silk materials.

BRITISH PETROLEUM

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British Petroleum (BP) was founded in 1909 as Anglo–Persian Oil Co., operating in what is now Iran. Today, BP is the second-largest publicly traded oil company in the world and the fourth-largest U.S. refiner. Despite the U.S. Gulf of Mexico Deepwater Horizon catastrophe (resulting in large fines, lawsuits and the sale of noncore assets), BP remains well positioned in the energy market with strong reserve replacements and growth prospects. Also, BP is the second-largest producer of gas in the U.S.

BP is actively involved in developing renewable energy, and the company has funded multiple R&D and commercialization activities. BP was an early investor in synthetic biology, by providing $500 million to University of California, Berkeley, and $50 million to MIT to investigate biologic and thermochemical pathways, respectively.

In 2006, BP formed a joint venture with DuPont, called Butamax Advanced Biofuels LLC, to develop and produce biobutanol. Butamax built a pilot facility to product butanol from sugar and starch crops; this plant is currently idle.

In November 2013, BP announced two new platforms for producing key petrochemical feedstocks. One is SaaBre, for producing acetic acid from synthesis gas. The other is Hummingbird, which converts ethanol to ethylene through dehydration.

BRISTOL-MYERS SQUIBB

345 Park Avenue
New York, NY 10154
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Website: www.bms.com

Bristol-Myers Squibb is a global drug manufacturer, with an emphasis on cardiovascular, anti-infective and anticancer therapies.

In synthetic biology, Bristol-Myers Squibb is a leader in cancer immunotherapies, and is developing checkpoint inhibitors for multiple cancer types. Opdivo, one of these inhibitors, enables T cells from the immune system to attack cancer tumors. This drug was approved by the FDA in December 2014 for treating patients with metastatic melanoma, treated patients with advanced renal cell carcinoma and previously treated nonsquamous and squamous nonsmall cell lung cancer.

Bristol-Myer Squibb's Genome Biology and Emerging Technologies group is evaluating and developing emerging genomic-engineering technologies for the drug-discovery workflow.

CALYSTA INC.

1140 O'Brien Drive
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Calysta Inc., a spinout from ATUM (formerly DNA2.0) in 2011, is using DNA2.0's gene and enzyme engineering platforms to develop methanotrophs, naturally occurring bacteria that feed on methane.

In June 2013, Calysta formed an alliance with NatureWorks. The two companies will work on transforming methane into lactic-acid building blocks for plastics.

In May 2014, Calysta acquired BioProtein A/S (Norway), extending the market for Calysta's methane conversion technology to the fish and animal feed markets.

In January 2016, Calysta commissioned its Market Introduction Facility for FeedKind protein, a fish-feed ingredient designed to reduce the use of fishmeal in the aquaculture industry. FeedKind protein is approved for sale in the E.U.

Calysta has an alliance with the University of Nottingham and Chain Biotech aimed at developing platforms for fermenting methane gas into omega 3 nutritional products.

CARGILL INC.

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Cargill Inc. is a major agribusiness company, with multiple product areas. The company's main businesses include: Agriculture Nutrition and Protein (customized farm services and products); Food Ingredients and Applications (food and beverage ingredients and meat and poultry products); Industrial; Origination and Processing (commodity origination, processing, marketing and distribution); and Industrial and Financial Services (physical products and risk management).

Cargill entered the synthetic biology business in April 2015 with its acquisition of OPX Biotechnologies Inc. The acquisition strengthened Cargill's fermentation-products businesses outside of food and feed.

OPX Biotechnologies Inc., founded in 2007 as a spinout from the University of Colorado, developed synthetic-biology technologies including new microbe strains for biorefining and next-generation biofuel applications.

OPX's strategy is to use E. coli as a microorganism platform for its synthetic-biology development. The company's synthetic-biology platform is called EDGE (efficiency directed genome engineering).

E. coli is an important bacterium used in fermentation reactions for making advanced biofuels and chemicals derived from biofuels. A key advantage of E. coli as a cell factory for biofuels is that it can convert a diverse variety of feedstocks, including sugars. Modifying E. coli for biofuel production involves multiple genes and genetic pathways, making a synthetic-biology toolbox important for using the bacterium. The OPX technology platform allows one to simultaneously study millions of genetic changes and assess how they affect production rate and efficiency.

OPX uses a massively parallel approach to identify the relevant genes of E. coli and test gene modifications to achieve metabolic pathways required for production of fuel and chemical products. The key to this technology platform is its speed, which is reported to be one to two orders of magnitude faster than conventional synthetic-biology techniques. The result is new microbial cell factories that give improvements in tolerance, productivity and specificity.

The company is actively involved in developing methods and tools for strain engineering, approaches for understanding library enriched microbial cell factories and engineering immobilized cell reactors for biofuels.

OPX's IP covers a broad host range of plasmid vectors, mixed library parallel gene-trait mapping, growth-enhancing genes, ethanol tolerance genes in E. coli and novel tools for linking screens with selections.

CARIBOU BIOSCIENCES INC.

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Website: www.cariboubio.com

Caribou Biosciences Inc., founded in 2012, is developing and commercializing genome-editing technologies based on Cas enzymes. The company's lead product, Cas9 enzyme, is a gene-editing platform that enables multiplex genome engineering through targeting multiple genomic sites in a single experiment.

In May 2016, Caribou partnered with Genus PLC, a leader in animal genetics. The agreement gave Genus exclusive license to Caribou's CRISPR/Cas9 platform for livestock species. The intent is to develop new traits for pigs, cattle and other livestock species. The agreement is for four years of R&D, with an extension option for three years. An initial target will be developing and optimizing Genus' porcine reproductive and respiratory syndrome virus (PRRSv)-resistant pigs.

PRRSv causes persistent infection in pigs and results in reproductive failure, reduced growth and premature death. The disease affects millions of pigs and piglets each year, and it has no cure. In the CRISPR/Cas9 approach to PRRSv, a single pig gene is inactivated. This gene produces the protein CD163, which the PRRSv needs for infection to happen. The alliance extends the CRISPR/Cas9 platform to the livestock market.

In February 2016, Caribou formed a collaboration with Integrated DNA Technologies (IDT) in which Caribou granted to IDT global rights to commercialize CRISPR/Cas9 reagents. This partnership will allow life science researchers with the appropriate tools for their synthetic-biology research.

In October 2015, Caribou formed a partnership with DuPont, which included cross-licensing of IP, joint research and financial investments by DuPont in Caribou. As both Caribou and DuPont have patent portfolios covering CRISPR/Cas9 technologies, this agreement enables Caribou to expand its product development in multiple market segments such as diagnostics, human and animal therapeutics, industrial biotechnology, research tools and agriculture.

In January 2015, Caribou formed a partnership with Novartis covering the development of CRIPS/Cas9 systems for use in drug-target-screening and validation technologies. This agreement expanded the applications field for Caribou's CRISPR/Cas9 technology to the field of drug discovery.

CELL DESIGN LABS

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Cell Design Labs, founded in 2016 as a spinout of the University of California, San Francisco, is using synthetic-biology tools – molecular control modules – to genetically engineer human cells to be able to sense and disable targeted diseases.

The initial clinical application that the company is targeting is immune cancer. Cell Design Labs is applying its on–off switches and synthetic Notch receptor tools to enhance the capabilities of T cells for fighting cancers.

In June 2016, Cell Design Labs formed an alliance with Kite Pharma Inc. to develop CAR (chimeric antigen receptor) therapeutics that use Cell Design's on–off switch technology. Kite, which has a pipeline of CAR-T-cell products, received an exclusive license to develop and commercialize CAR-T-cell therapies that incorporate Cell Design's on-off switches for treating acute myeloid leukemia. The agreement also gave Kite the exclusive option to develop and commercialize CAR-T-cell therapies using on–off switches for treating B-cell malignancies.

The alliance provides Kite with synthetic-biology tools that can increase the activity and/or improve the safety of its engineered T-cell therapy candidates.

CELLECTIS SA

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Website: www.cellectis.com

Cellectis SA, founded in 1999, is a gene-editing company whose main business focus is on developing immunotherapies based on re-engineered CAR-T cells. Cellectis' lead product is UCART19, an allogeneic CAR-T-cell therapy for treating chronic lymphocytic leukemia and acute lymphoblastic leukemia. This program is partnered with Servier.

The clinical advantage of the allogeneic approach is that it uses T cells from healthy third-party donors. The strategy is to insert this CAR gene and inactivate other genes to add desirable features to the T cells, such as minimizing the risk of graft-versus-host disease. Compared with autologous CAR-T cells, this approach has several potential benefits: good quality control of CAR-T-cell production; rapid availability to the patient (for autologous strategies the patient must have a ready source of harvestable T cells and it may take as long as three weeks for the cells to be processed and reinfused); and minimal cost (about $125,000 per patient versus $500,000 for autologous technologies).

Cellectis also is developing three therapies on its own, including UCART123, UCART38 and UCARTCS1.

In addition to its immunotherapy business, Cellectis is using its gene-editing platforms to develop improved crops and/or food through its Calyxt plant sciences division.

In Cellectis' Calyxt division, field trials are being pursued for reduced-trans-fat soybean and long-storage potatoes. The U.S. Department of Agriculture (USDA) has given nonregulated status to these products, thus shortening the development time.

Cellectis uses TALEN for its gene-editing approach. This is combined with PulseAgile (electroporation in which electric pulses generate pores in cell membranes to allow for molecules to pass through). The combination of these technologies allows for specific, precise and efficient gene modifications.

CHAIN BIOTECHNOLOGY LTD

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Chain Biotechnology Ltd., founded in 2014 as a spinout from the Imperial College and the University of Nottingham, is developing a Clostridium bacteria production platform for a range of biotechnology applications. The company is using synthetic-biology methods to generate unique industrial strains of the bacterium.

The company's platform relies on modular shuttle plasmids, in which each plasmid contains one module of each of four types, which are always arranges in the same order and always bounded by the same four rare (8 base pair [bp]) type II restriction enzyme recognition sites. This platform enables shuttle plasmids to be created from modules in standard formats.

Advanced synthetic-biology tools, including gene knock-out and integration, gene expression and transposon mutagenesis, are used to engineer bacteria to produce high yields of natural products or novel products from a wide variety of feed stocks.

CIBUS INC.

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Cibus Inc., founded in 2001, is a genome-editing company that is developing and commercializing a nontransgenic breeding platform, Rapid Trait Development System (RTDS).

RTDS is a system combining aspects of cell biology, precision gene editing, molecular screening, breeding and crop development. The central aspect of this technology is the gene repair oligonucleotide (GRON), which is designed to hybridize to a targeted gene region in the plant DNA. The GRON creates a mismatch with the plant DNA sequence, and the plant's native repair enzymes recognize and fix the DNA, using the GRON as a template. This GRON is removed after the repair is completed and is digested by the plant cell. The end result is that the targeted gene now has a change in its sequence, which can create a valuable plant characteristic, such as herbicide resistance.
Cibus' first product, SU Canola, is a nontransgenic canola tolerant to sulfonylurea herbicides. SU Canola was launched in the U.S. in 2016 and received regulatory approval for Canada.

Cibus is developing a range of nontransgenic traits for many of the major crops.

CODEXIS INC.

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In 2002, Maxygen spun off Codexis Inc. as a wholly owned subsidiary with a goal of replacing multistep manufacturing of high-value pharmaceutical and chemical products with simplified processes.

Since then, Codexis has raised significant amounts of venture funding, and Maxygen's share of ownership has decreased as a result. Codexis retains a license to use Maxygen's molecular-breeding directed-evolution platforms for certain applications relating to energy, including biofuels.

Codexis is focused on a synthetic-biology platform that can develop enzymes for specialized purposes. The company's platform, called Code Evolver, creates libraries of gene variants encoding biocatalysts with novel functions. This gene-variant library is then recombined, or shuffled, creating new variants. The resulting DNA sequences are screened for novel catalytic function as part of directed-evolution programs. High-throughput screening methods are used to select those sequences with desired phenotypes.

Codexis is focusing on the pharmaceutical business, after it terminated its collaboration in biofuels with Royal Dutch Shell in 2012.

Partners in pharmaceuticals include GlaxoSmithKline, Exela, Merck & Co and Pfizer. In August 2015, Codexis formed a partnership with Merck & Co. As an outcome of this, Merck is using Codexis' platform to develop biocatalysts for Januvia (diabetes) and active ingredients for its hepatitis C products.

DEMURIS LIMITED

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Demuris Ltd. has developed a pipeline of antibiotics that are produced by actinobacteria. The lead candidate is produced by an organism that is not suited to large-scale fermentation, and the molecular structure is not yet optimal for pharmacological properties.

In January 2013, Demuris began working with the John Innes Centre to use synthetic-biology technologies to improve production of the lead antibiotic candidate. The approach is to identify the antibiotic producer gene cluster and re-engineer for production in a better chassis.

In August 2013, Demuris was awarded a grant from the Technology Strategy Board (U.K.) of approximately $900,000. The grant covers the use of synthetic-biology tools to identify and refactor the gene cluster for optimizing production of broad spectrum antibiotics and to create antibiotics with improved properties.

In April 2016, Demuris began a collaboration with Dundee Cell Products to develop synthetic-biology approaches to discovering and exploiting previously unseen antibiotics from existing libraries.

DESKTOP GENETICS LTD.

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Desktop Genetics Ltd., founded in 2012, is developing and marketing software solutions for the synthetic-biology industry.

Desktop Genetic’s software product was AutoClone, launched in 2013. AutoClone is an automated program for designing, constructing, managing and exchanging DNA constructs that are used in synthetic-biology workflows.

In 2014, Desktop launched Guidebook, a CRISPR design tool that uses gene-editing techniques to provide optimal design for genome-editing experiments. In 2015, Desktop

launched DeskGen, a software package for designing genome-editing experiments with any cell line and for generating CRISPR libraries.

DOW CHEMICAL COMPANY

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The Dow Chemical Company is a large diversified chemical company and the largest U.S. chemical company. The company is global in scope, with more than 67% of 2014 sales outside North America. Major businesses include: Consumer Solutions (9% of 2015 sales); Infrastructure Solutions (15%); Performance Materials and Chemicals (25%); Performance Plastics (38%); and Agricultural Sciences (13%).

In July 2016, the stockholders of both Dow Chemical and DuPont voted to approve the merger of the two companies. Following the completion of the merger, the combined company will work toward separating out three separate businesses: Agriculture, Materials Science, and Specialty Products. The Agriculture business should be a key developer and user of synthetic-biology tools and products.

Dow activities in the synthetic-biology industry are highlighted by recent collaborations of Dow AgroSciences with several companies, including Radiant Genomics and TeselaGen Biotechnology Inc.

In February 2016, Dow AgroSciences formed an alliance with Radiant Genomics, a synthetic-biology company. The collaboration will focus on developing new products derived from naturally derived chemistries. They will use Radiant’s synthetic-biology and metabolic-engineering platforms and Dow’s natural/product discovery and product development expertise.

In April 2016, Dow AgroSciences formed an alliance with TeselaGen Biotechnology Inc. This collaboration will enhance Dow’s synthetic biology development workflow by adding software capabilities in designing and editing DNA.

E.I. DU PONT DE NEMOURS AND COMPANY

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E.I. du Pont de Nemours and Company (DuPont), a large diversified chemicals company, is the second-largest chemical producer in the U.S.

Major business units include agricultural (39.0% of sales in 2015), nutrition and health (13.0%), industrial biosciences (4.7%), electronic and communication technologies (8.2%), performance materials (21.1%) and safety and protection (14.0%).

DuPont has a major focus on using renewable feedstocks to produce products that have equal or better performance than existing products and a smaller environmental footprint. Biomaterials based on new processes include Cerenol polyols and the polymer Sorona. The company views strategic future markets for biomaterials in lubricants, coatings and cosmetics.

DuPont became a major synthetic-biology company through its purchase of Danisco in 2011, and also through its strategic alliances with Goodyear (synthetic production of rubber) and OligoCo (DNA-synthesis technologies).

DuPont's Industrial Biosciences business segment includes many of its synthetic-biology activities, including Danisco (food ingredients and industrial enzymes), Sorona (renewably sourced polymer) and bio-PDO.

DuPont is the world's leading producer of corn, soy seed and crop protection products and has an extremely strong agricultural business. These businesses provide exceptional synergy with synthetic-biology-based markets in biofuels, chemicals and pharmaceuticals, as feedstocks are a critical part of the value chain for biomaterials. For example, DuPont's Pioneer business unit is a major participant in hybrid corn and soybean seeds. This unit is using advanced genomics tools to optimize the yield of ethanol from corn and biodiesel from soybeans.

In April 2016, DuPont announced that it would develop and commercialize a corn product that has been genetically modified with CRISPR/Cas9. The USDA indicated to DuPont that it would not regulate this CRISP-modified corn product to the same rules as for conventional GMOs.

In October 2015, DuPont formed a strategic alliance with Caribou Biosciences, which involves IP cross-licensing of CRISPR/Cas technologies owned by each company. The companies will also collaborate on research involving gene editing and crop development.

DuPont's biofuel strategy is to enhance existing ethanol production using its agricultural seed products, use synthetic-biology tools to enable cellulose to ethanol conversion and scale-up next-generation biofuels that have improved performance.

DuPont operates a cellulosic ethanol plant in Nevada, Iowa. The plant has a capacity of 30 million gallons of ethanol per year.

In December 2015, DuPont acquired the C1 industrial enzyme assets of Dyadic. Dyadic continues to have co-exclusive rights to the C1 technology for pharmaceutical applications. C1 is licensed to Agengoa (cellulosic ethanol production), BASF (animal feed, food, textile production) and Sanofi Pasteur (vaccine, antibody and therapeutic protein production).

This acquisition complements DuPont's 2011 acquisition of the industrial enzyme company Danisco.

DYADIC INTERNATIONAL INC.

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Dyadic International Inc., founded in 1979, is a biotechnology company that focuses on developing and commercializing novel enzymes for applications including energy production. The company's key product is C1, a fungal microorganism Chrysosporium lucknowense, which can be used to discover and express prokaryotic or eukaryotic genes.

Dyadic's technology platform uses C1, high-throughput screening and enhanced protein-expression systems. This synthetic-biology-based platform provides an end-to-end workflow for gene discovery, expression, product development and manufacturing.

In December 2015, Dyadic sold the assets of its industrial biotechnology division to DuPont. The company refocused its applications efforts in the biopharmaceuticals business at that time.

EDITAS MEDICINE INC.

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Editas Medicine Inc., founded in 2013, is using CRISPR/Cas9 genome-editing technology to develop therapies for patients with genetically defined diseases. The initial development focus is on severe genetic diseases that have no approved treatments. This group of diseases comprises more than 6,000 types, which are caused by a genetic mutation, and approximately 95% have no approved therapy. Examples of targets include muscular dystrophy, cystic fibrosis (CF), hematologic diseases and liver direct targets.

The first disease being targeted by Editas is Leber congenital amaurosis, an inherited retinal dystrophy that affects the retina and lead to blindness. Clinical testing is expected to start in 2017. This program is relatively low risk because the eye is a closed system, making delivery probable and off-target toxicity unlikely. Also, only a small percentage of the photoreceptors in the eye (10% to 20%) need to be edited to provide some vision.

Editas' pipeline consists of LAC10, other diseases of the eye, T cell for treating cancer, nonmalignant hematological diseases, genetic diseases of the muscle and lung, and genetic and infectious diseases of the liver. With the exception of LAC10, these programs are in the discovery stage.

In May 2015, Editas formed an alliance with Juno Therapeutics Inc. for development of CAR- T and high-affinity T-cell receptor (TCR) cancer therapies. The collaboration will use

Editas' genome-editing technologies (CRISPR/Cas9) and Juno's CAR and TCR technologies in the development program.

ENBIOTIX INC.

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EnBiotix Inc., founded in 2012 as a spinout of Boston University, is using synthetic-biology technology to develop engineered bacteriophage (phage) products for antibacterial markets.

EnBiotix has several products in preclinical development, including EBX-001 and EBX-002. EBX-001 is being developed to be given together with tobramycin for Pseudomonas aeruginosa infections among CF patients. Up to 80% of all CF patients develop chronic P. aeruginosa infections by the age of 25. The antibiotic tobramycin, given as an inhaled product, is a key therapy used today, with all 10 drugs derived from this antibiotic. Tobramycin has been available in generic inhaled form since late 2013.

EBX-002 is being developed to target gram-negative persisters in hospital patients with indwelling urinary catheters.

In addition to these two products, EnBiotix is developing an engineered bacteriophage platform, called engineered phage products (EPPs) for a range of biofilm indications. The lead product, EPP-001, is a bacteriophage that can induce target bacteria to produce an enzyme that destroys a bacteria-based biofilm. The target market for this therapy is treating infections in prosthetic joints.

ENEVOLV INC.

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EnEvolv Inc. is using synthetic-biology tools to develop new genome-engineering technologies. The company's platform, Multiplex Automated Genome Engineering (MAGE), allows large-scale genome modifications to be made at multiple locations at the same time.

Using MAGE, EnEvolv engineers unique microorganisms (e.g., bacteria, yeast and algae) or improves existing strains to increase production yield and product quality. The company licenses these microorganisms to industry.

EPOCH LIFE SCIENCE INC.

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Epoch Life Science Inc., founded in 2002, is a molecular-biology reagents company with an emphasis on nucleic acid purification kits, modifying enzymes, cytokines, antibodies and DNA synthesis. Epoch provides gene-synthesis services that include fragment synthesis, cloning, codon optimization and sequence verification. Total annual sales for the company are estimated at less than $5 million.

Epoch is positioning its gene-synthesis service as an alternative to cloning among its academic and industrial research customers. The company emphasizes the cost savings by eliminating the messenger RNA (mRNA) extraction, reverse transcription (RT)-PCR, and cloning or subcloning steps. Potential cost savings over conventional cloning based on Epoch's synthesis pricing structure are 33% for a 2 kb, less than 10 copy, lower than 50% GC (guanine–cytosine) sequence.

The company is a second-tier competitor in the gene-synthesis market.

EUROFINS MWG OPERON

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Website: www.operon.com

Eurofins MWG Operon was founded in 1990 and is a member of the Eurofins Group, a global provider of genomic services. The company provides DNA-sequencing services, oligonucleotide and gene synthesis, and small-interfering-RNA tools. Originally called MWG Biotech, in December 2004 the company became a member of the Eurofins Scientific Group. MWG, Medigenomix and Operon form the genomic services businesses of the Eurofins Group.

A main competitive strategy for gene-synthesis companies is proprietary bioinformatic services for optimizing gene design. MWG Operon uses bioinformatics as a key part of its positioning in the high-quality, value-added synthetic-gene market segment. The company uses automatic codon-optimization software to optimize gene synthesis. For standard genes, key features that must be controlled include: moderate GC content (40% to 65%); repeats (repeats greater than 20 bp not allowed); critical hairpin structures (not allowed); and homopolymer stretches (stretches greater than 20 bp not allowed).

MWG Operon participates in the standard and complex gene market segments, as well as selling gene-evolution libraries.

In June 2013, Eurofins acquired Entelechon GmbH (Germany). The company is being integrated into Eurofins' MWG Operon's gene-synthesis business. This acquisition provides complementary services in the growing synthetic-biology market.
A leading synthetic biology software platform offered by Eurofins is Genius 2.0, which optimizes and adapts amino acid or DNA sequences. The main advantages of this platform include reducing rare codons in the expressing organism, excluding unwanted secondary structures (e.g., repeat and hairpin) and spreading out the distribution of G and C bases.

Entelechon provides a wide range of tools that are useful to synthetic biology: software for the optimization of DNA sequences for maximizing expression levels; DNA synthesis including genes and long polycistronic constructs, microarray design; and protein-expression and quantification technologies. An important differentiator among gene-synthesis companies is Entelechon's position in bioinformatics, DNA synthesis and proteomics. Proteomics technologies can be combined with gene synthesis to create an optimized gene for maximum expression yields.

Entelechon has a strategic partnership with Plasmid Factory, Europe's largest manufacturer of plasmid DNA. Plasmids are an important part of the gene-synthesis value chain. With this partnership, Entelechon is able to synthesize large quantities of genes and ship them in plasmid form to customers.

In March 2016, Eurofins formed an alliance with Agilent Technologies in which Agilent's SureVector cloning kits will be offered by Eurofins. SureVector kits allow researchers to make customized vectors (small DNA molecules within cells that can replicate independently) from standard components. The SureVector product line complements Eurofin's gene-synthesis services.

Agilent's molecular-biology tools address the entire workflow for synthetic biology.

EVOLVA SA

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Website: www.evolva.com

Evolva SA, founded in 2004, is developing and commercializing a yeast synthetic-biology platform for producing nutritional and consumer health products. Evolva's strengths include a diverse product pipeline and multiple industry alliances with leading companies, including Cargill, L'Oréal and Takasago.

Evolva's main near-term ingredient products include vanillin, nootkatone, resveratrol and stevia. The company has also shifted from its earlier, historic focus on pharmaceutical products toward consumer health and nutrition products.
In 2014, Evolva launched its vanillin product through its partner International Flavors and Fragrances. In 2015, Evolva launched its nootkatone product, a citrus flavoring.

Evolva is partnered with Cargill to commercialize its stevia sweetener products. In the stevia sweetener market, there is a need for improving on the current Reb A, which is bitter and has a licorice aftertaste. Reb D and Reb M, while tasting better than Reb A, are found in very tiny concentrations in the stevia leaf (less than 1%).

The objective is to produce Reb D and Reb M (trade-named EverSweet) at an economical cost and introduce these into the market. Evolva is also tapping into the increasing demand for natural sweeteners with this product. During 2015 and 2016, Coca-Cola, Dr. Pepper and Pepsi launched stevia-sweetened drinks, to meet the demand for natural sweeteners in low-calorie drinks.

Stevia is an example of the potential power of using synthetic biology for fine chemical production. Using synthetic biology, Evolva has engineered the yeast genome to produce mostly Reb D, which is sweeter and more suitable for drinks and other foods.

Evolva’s synthetic-biology platform, called genetic chemistry, consists of genetically modifying yeast cells, which produce chemicals and drugs that can be selected for further development. The table below illustrates this platform.

TABLE 114

EVOLVA'S GENETIC CHEMISTRY PLATFORM

Step	Description
Create a set of YACs	Hundreds of genes from various organisms are randomly assembled into millions or billions of unique YACs
Insert YACs into yeast cells	YACs are inserted into haploid yeast cells and then bred together to make a complete library
Yeast cells produce chemicals	Novel combinations of enzymes produced by the genes in each YAC generate multiple chemicals, some of which are valuable
Select cells of interest	Selection is done by either fluorescence or survival in the presence of toxins when a specific chemical is produced
Identify market of interest for chemical	Cells are analyzed by genomic or proteomic methods to identify drug candidates or enzymes needed for producing a specialty chemical of interest

YAC, yeast artificial chromosome.

Source: BCC Research

The technology enables Evolva to screen a large number of yeast cell lines that contain unique combinations of genes from other organisms. Those cell lines that are selected out from this process can produce unique drugs or specialty chemicals of interest.

In November 2014, Evolva acquired Allylix, which strengthened Evolva’s position in biosynthetic production.

Allylix uses protein (terpene cyclase) engineering and yeast metabolic engineering technologies to produce terpene specialty chemicals. Terpenes, used in flavors and fragrances, insect repellents and biocides, are available naturally in small quantities. A

synthetic production platform will make them available in larger quantities and at reduced prices.

Allylix's technology platform includes synthetic engineering of very pure terpenes, as well as proprietary fermentation processes to cost-effectively produce those terpenes.

The initial products launched by Allylix include nootkatone and valencene, which give the aroma of grapefruits and oranges to perfumes and cosmetics. Besides use in flavors and fragrances, nookatone provides skin and home protection against pests such as mosquitoes, bed bugs or ticks.

These products are complementary to Evolva's product line, and are high-value ingredients produced from yeast. Thus, this acquisition strengthened Evolva's position in yeast-based fermentation technologies.

EVONETIX

29 Cambridge Science Park
Cambridge CB2 0DW
U.K.
Tel: 44-1223-392650
Website: www.evonetix.com

Evonetix, founded in 2016 as a spinout from the University of Cambridge, is developing and commercializing technologies for low-cost, high-fidelity DNA synthesis.

This technology is differentiated from other next-generation synthesis technologies by permitting longer, highly accurate DNA strands for low cost.

EXXONMOBIL CORP.

5959 Las Colinas Boulevard
Irving, TX 75039
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Fax: 972/444-1433
Website: corporate.exxonmobil.com/

ExxonMobil Corp., created in 2009 with the merger of Exxon and Mobil, is the largest publicly traded integrated oil company in the world. Revenues include oil and natural gas exploration and production ($27.5 billion in earnings in 2014), refining and marketing ($3.0 billion), chemicals ($4.3 billion) and other operations, including electric power generation, coal and minerals.

In August 2009, ExxonMobil formed an alliance with Synthetic Genomics to produce oil from engineered strains of algae. ExxonMobil committed to $600 million for funding its internal costs and Synthetic Genomics' research. This alliance did not produce positive results, and ExxonMobil cut back its support in 2013.

GEN9 INC.

840 Memorial Drive
Cambridge, MA 02139
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Fax: 815/425-8745
Website: www.gen9bio.com

Gen9 Inc., founded in 2012, is developing and commercializing a portfolio of next-generation gene-synthesis technologies that allow high-throughput, automated manufacturing of DNA constructs. The company's proprietary DNA fabrication platform, BioFab, combines small DNA fragments with proprietary chemical processes that assemble them into larger DNA strands.

In June 2013, Gen9 launched its GeneBytes DNA constructs (gene fragments of length from 1,000 bp to 4,000 bp long). GeneByte Plus are constructs 4,000 bp to 10,000 bp long. Gen9's product portfolio also includes GeneBits constructs, which are shorter DNA lengths ranging from 500 bp to 1,000 bp.

GeneBits, GeneBytes and GeneBytes Plus DNA constructs are manufactured as clonal, sequence-verified DNA and can be shipped either as linear double-stranded DNA (dsDNA) or cloned into vectors.

The introduction of GeneBytes and GeneBytes Plus is part of a recent trend in the gene-synthesis industry toward offering linear gene-synthesis products. This is shown in the table below.

TABLE 115

LINEAR GENE-SYNTHESIS PRODUCTS

Company	Product	Maximum Length (bp)
Gen9	GeneBytes, GeneBytes Plus	10,000
IDT	gBlocks	2,000
Life Technologies	Strings	3,000

IDT, Integrated DNA Technologies.

Source: BCC Research

Pricing depends on volume. For example, Gen9 offers three tiers of pricing for its Multiplex Access Partnership (MAP) program customers. The price for two or more megabases is $0.08 per bp, for 10 or more megabases is $0.05 per bp and for 50 or more megabases is $0.03 per bp.

In February 2016, Gen9 launched its MAP program, which gives partners access to Gen9 synthetic DNA. In April 2016, Arzeda joined this program, giving it access to DNA for its cell-factory-based business. In June 2016, Ginkgo Bioworks reached an agreement with Gen9 for supply of 300 million bp of long-length synthetic DNA. Ginkgo will use this DNA in

its synthetic-biology-foundry operations. In June 2016, Amyris reached an agreement with Gen9 for supply of large quantities of synthetic DNA for use in Amyris' production processes.

GENEMED SYNTHESIS INC.

6203 Woodlake Center, Building No. 2
San Antonio, TX 84244
Tel: 210/745-5988
Fax: 210/569-6374
Website: www.genemedsyn.com

Genemed Synthesis was founded in 1987. The company focus is on protein and peptide sequencing for determining protein structure and PCR reagents including primers and probes.

Genemed Synthesis has also synthesized genes for the past 10 years using its own proprietary technologies.

GENE ORACLE INC.

500 Laurelwood Road #6
Santa Clara, CA 95054
Tel: 408/520-7703
Website: www.geneoracle.com

Gene Oracle provides software tools for gene synthesis. The company's lead product, GeneIOS Version 2.1, allows researchers to rapidly make synthetic genes that are up to 1 kb in length. GeneIOS included GeneScreen and GenePerfect.

GeneScreen is a software program that analyzes the synthesizability of any DNA sequence by searching for complementary repetitive elements, direct repetitive elements and polynucleotide strings.

GenePerfect works together with GeneScreen to remove regions of a prospective sequence that may slow or inhibit synthesis, to optimize coding sequences for protein expression and DNA stability.

The company provides a gene-synthesis service, FastaDNA, to life science researchers in the biotechnology and pharmaceutical industries.

GENEWORKS PTY. LTD.

28 Dalgleish Street
Thebarton, South Australia 5031
Australia
Tel: 61-8-8159-6250
Website: www.geneworks.com.au

GeneWorks, founded in 1996, supplies molecular-biology research products, with a core business in oligonucleotides. GeneWorks has a regional focus in Australia and New Zealand.

The company is a second-tier supplier of synthetic genes and custom oligonucleotides.

GENOMATICA

4757 Nexus Center Drive
San Diego, CA 92121
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Website: www.genomatica.com

Genomatica, founded as a spinout from the University of California, San Diego, employs synthetic-biology tools to create new organisms and manufacturing processes for bioproducts. The company's lead product is BDO.

The global market for BDO is 2.8 billion pounds per year, worth an estimated $4 billion. The product is currently manufactured by industry as a multistep process using petroleum-derived feedstocks including acetylene, propylene oxide and butadiene. BDO is used to produce solvents, fine chemicals and high-performance polymers (spandex fibers, engineered plastics, protective casings and soles of running shoes).

Genomatica's main strategic partner is DuPont (Tate & Lyle). In February 2013, Genomatica announced that it had begun producing BDO in 600,000-liter fermenters at the Tate & Lyle plant in Tennessee. The plant is producing approximately 140 million pounds of BDO per year. The feedstock is dextrose sugars. This represents the first commercial production of bio-based BDO.

Genomatica's fermentation technology for producing bio-BDO is being commercialized by Novamont (30,000 tonnes per year plant in Adria, Italy) and BASF (75,000 tonnes per year plant).

In July 2013, Genomatica signed a multiyear licensing agreement with TeselaGen giving Genomatica access to CAD software for synthetic-biology approaches for building and modifying DNA. This agreement will help to accelerate Genomatica's development of synthetic-biology-modified microorganisms.

A second product for Genomatica is butadiene, which has a growing $20 billion global market.

In December 2013, Genomatica formed a partnership with Braskem (Brazil) for production of commercial quantities of bio-based butadiene. Braskem is the world's largest producer of biopolymers and the world's third-largest butadiene manufacturer. This partnership has been successful in producing butadiene at the laboratory scale during 2015.

In April 2013, Versalis formed a joint venture with Genomatica covering the funding of development efforts for butadiene. The companies will work together to develop a complete production process dedicated to butadiene from nonfood biomass feedstocks. Versalis brings expertise in downstream operations including catalysis and process

engineering. In February 2016, the companies announced pilot-scale production of biobutadiene using the Genomatica technology. The biobutadiene was then used to produce biopolybutadiene (biorubber).

In July 2015, Genomatica formed an alliance with Cargill, which gave the users of Genomatica's technology access to Cargill's carbohydrate feedstocks and support services. Cargill is also able to build and operate bio-based chemical plants that use the Genomatica technology.

GENSCRIPT

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China
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Website: www.genscript.com

GenScript, founded in 2002, manufactures and markets genomic and proteomic tools for the life sciences industry. The main business areas include: life science research services (90% of 2015 revenue); preclinical drug development services (6%); life science research catalog products (3%); and synthetic-biology products (1%).

Life science research services include: DNA synthesis, genetic analysis and engineering services; recombinant protein production; peptide synthesis and customized antibody production; and biochemical reagents and research kits.

The DNA-synthesis market is important to GenScript, and it has a leading position in terms of market share. For gene synthesis, GenScript is the global leader with the highest market share. GenScript has developed several other business related to DNA synthesis, including DNA-sequencing services (for confirming the fidelity of the sequence for DNA-synthesis constructs) and production of downstream proteins from the genes that are synthesized.

In 2014, GenScript began to product downstream synthetic-biology products, including industrial enzymes. This business is a key growth strategy for the company, as it is complementary to its legacy businesses of developing and synthesizing new genes.

GEVO INC.

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Website: www.gevo.com

Gevo, founded in 2005 as a spinout from the California Institute of Technology, is developing biofuels and renewable chemicals using a synthetic-biology technology approach. The company is focused on commercializing isobutanol. Isobutanol's main applications include as a solvent and a gasoline blendstock, which can be further processed into jet fuel and feedstocks for producing synthetic rubber.

Gevo operates an isobutanol production plant in Laverne, Minn. In early 2016, the plant underwent a significant improvements renovation to decrease the cost of producing isobutanol and in May 2016 was restarted.

In June 2016, Gevo announced that it had an agreement with Musket Corp. covering the supply of isobutanol for blending in gasoline. Musket is a fuel distributor that operates throughout the U.S. The agreement scope includes the marine and off-road markets in Arizona, Nevada and Utah.

Isobutanol offers several advantages as an additive in the marine gasoline market. Blending helps to prevent moisture absorption and phase separation and to reduce engine corrosion; it also imparts a higher energy content, and the blended gasoline has a higher octane rating.

Another key market for isobutanol is as an additive in jet fuel. Gevo is working with Alaska Airlines to test its alcohol to jet fuel (ATJ) product in actual test flights. The objective is to use ATJ as a blending component in standard Jet A-1 or commercial airline flights, in up to a 30% blend. The advantage to the airlines is that this reduces greenhouse gas footprint and reduces particulate emissions from combustion.

GINKGO BIOWORKS

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Boston, MA 02210
Tel: 814/422-5362
Website: www.ginkgobioworks.com

Ginkgo Bioworks, founded in 2008 as a spinout from the Massachusetts Institute of Technology, is designing and operating production systems using designed organisms. Ginkgo is developing organisms that can produce a range of products, including flavors and fragrances, industrial enzymes, nutritional ingredients, cosmetics, sweeteners and pharmaceuticals.

Ginkgo works with companies in end-product areas to design the microorganism, and develop a production method for producing the end product. Ginkgo derives revenues from royalties on sales of the final end product. Examples of end-use customers that Ginkgo works with include Anjinomoto (food and pharmaceuticals) and Robertet (flavor and fragrances).

Robertet's objective in working with Ginkgo is to develop a less expensive and time-consuming path to producing a rose scent. The current method of doing this is to squeeze oils from the rose flowers' petals. In addition to rose scent, Ginkgo will also work on apricot, coconut and mango fragrances under its alliance with Robertet.

The workflow process that Ginkgo uses is described in the table below.

TABLE 116

ENGINEERED-ORGANISM WORKFLOW

Step	Description
Design DNA sequence	DNA code functions as the biologic instructions for the microbe
Order synthetic DNA	An outside firm specializing in DNA synthesis manufactures the specified DNA sequence
Insert DNA into microbes	
Culture microbes in a bioreactor	Genomically altered microbes produce end product

Source: BCC Research

Ginkgo's platform, called integrated organism engineering platform, is a set of tools (software, hardware, wetware) that organism engineers can use to build a microbe to specification for a customer. The end product is an engineered microbe. Ginkgo assists customers in deploying an engineered microorganism to produce a product in the customer's end-use market.

Ginkgo agrees on a specification together with the customer, builds the microbe and then deploys it at the customer's site to produce a product for sale.

Ginkgo has built two foundries or factories that use living organisms to produce new products. Bioworks1 is a rapid prototyping foundry for custom organism design. Bioworks2 will expand existing capacity, use new automation tools and scale-up the capabilities of Bioworks1. Automated tools play an important role in these foundries. These tools are used for assembling DNA, transforming cells and collecting data on factory organisms.

In June 2016, Ginkgo formed a partnership with Amyris. The two companies plan to develop and scale-up production for more than twenty ingredients in cosmetics, jet fuel and industrial lubricants.

GLAXOSMITHKLINE PLC

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GlaxoSmithKline PLC (GSK) was created in 2000 with a merger between Glaxo Wellcome and SmithKline Beecham. GSK is the second-largest pharmaceutical company in the world.

In 2015, GSK sold its oncology assets to Novartis, and GSK now focuses on respiratory, HIV, vaccines and legacy drugs.

GSK is using synthetic-biology tools in two areas: production of small-molecule drugs and vaccine development.

GSK formed an alliance with Codexis in July 2014. In the agreement, Codexis licensed its CodeEvolver platform to GSK for the purpose of developing enzymes that can be used to manufacture small-molecule pharmaceuticals. In May 2016, Codexis successfully completed the transfer of this technology to GSK, triggering a milestone payment.

For vaccine development, viral material can be prepared and validated starting from viral gene sequences. These synthesized sequences can be inserted into a pre-existing viral backbone, transfected into eukaryotic cells in culture, and the virus harvested. Vaccine seed stock can be available in a day, versus up to six months via conventional methods.

GLOBAL BIOENERGIES

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France
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Website: www.global-bioenergies.com

Global Bioenergies, founded in 2008, creates artificial metabolic pathways to synthesize metabolic intermediates that are not found in nature. These pathways can be integrated into microorganisms to produce chemicals. The initial market focus is on isobutene, propylene and butadiene as well as other gaseous olefin family molecules.

The company’s first pilot plant is in France and has a 500-liter fermenter to produce 10 tons of isobutene per year.
In January 2014, Global Bioenergies partnered with Audi (Germany) to develop isobutene-derived isooctane for use in gasoline engines.

Isobutene has many applications, including conversion into isooctane, a key fuel for gasoline engines. Isooctane is a 100% drop-in fuel and can be used in any blending ratio with standard fuels for gasoline motors. Thus, it overcomes the limitations of ethanol or isobutanol, which require limited blending ratios and lower mileage per liter.

In July 2016, Global Bioenergies formed a partnership with IBN-One and Lantamannen Aspen covering the use of renewable isooctane for specialty fuel applications. Aspen gained rights to isooctane from the existing Launa demonstration plant and from the future IBN-One commercial plant. Aspen is a leader in agriculture, machinery, bioenergy and food products and uses specialty fuels in two- and four-stroke engines.

In May 2016, Global Bioenergies demonstrated good pilot-scale results from its fermentation trials. High yields (more than 65%) were sustained for several days, demonstrating a robust fermentation process.

GLYCOS BIOTECHNOLOGIES INC.

711 Leverkuhn Street
Houston, TX 77007
Tel: 713/869-9377
Fax: 713/869-2200
Website: www.glycosbio.com

Glycos Biotechnologies Inc. (GlycosBio) is developing microbes (mainly using E. coli) that can convert glycerin into biochemicals (e.g., lactic acid, isoprene) and neutraceuticals (e.g., enriched proteins, fiber, concentrated omega 3 and probiotics).

GlycosBio is focused on two main industries in its development efforts: specialty chemicals and health nutraceutical foods.

GOODYEAR TIRE & RUBBER CO.

200 Innovation Way
Akron, OH 44316
Tel: 330/796-2121
Fax: 330/796-2222
Website: www.goodyear.com

Goodyear Tire & Rubber Co. is the largest U.S. manufacturer of tires and among the largest globally. Key businesses of the company include rubber and plastic products and chemicals. Goodyear is a global company and has a dominant market share in North America, Latin America, China and India.

Goodyear worked with Danisco’s industrial enzyme synthetic biology group, Genencor (now DuPont), to develop isoprene using renewable feedstocks via synthetic E. coli. The collaborators developed an enzyme system that produces synthetic rubber and other elastomers, trade-named BioIsoprene, which DuPont supplies to Goodyear for use in tires.

GREEN BIOLOGICS LTD.

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Website: www.greenbiologics.com

Green Biologics Ltd. (GBL), founded in 2004, provides low-cost carbon chemical and fuels to chemical, sugar and ethanol producers. The company has developed microbial, fermentation and process technology that allows use of agricultural by-product feedstocks.

GBL uses synthetic-biology techniques to develop its Clostridium microbial platforms.

In December 2015, GBL began construction of a commercial production plant in Little Falls, Minn., which will produce n-butanol and acetone. This project is a significant milestone in GBL's efforts to become a global renewable specialty chemicals company.

In order to sell the production output from its Little Falls plant, GBL formed several strategic alliances in early 2016.

In March 2016, GBL partnered with Acme-Hardesty, which will market GBL's products in the food ingredients, cleaning products and biolubricants industries.

In April 2016, GBL formed a partnership with Nexeo Solutions, which will distribute GBL's n-butanol and acetone in the U.S. Nexeo, based in Texas, will focus its marketing efforts in the CASE (coatings, adhesives, sealants and elastomers), HI&I (household, industrial and institutional cleaners), PCI (personal-care intermediates) and energy chemicals industries.

GBL's approach is to market its commodity chemicals as specialty chemicals, emphasizing their high performance and natural ingredients to the end markets. For example, in the cosmetics and personal-care market, bio n-butanol can be used to produce natural oleic and palmitic acids. These natural products are free of contaminants, such as benzene, present in petroleum-derived products.

A key part of GBL's business strategy is to work with outside toll manufacturers of specialty chemicals industries to convert GBL's natural feed chemicals into high-value products, including dibutyl succinate, butyl acrylates, butyl acetate, butyl esters, amino resins, amines and plasticizers.

HELIX NANOTECHNOLOGIES INC.

Unit G5, 59 Chilton Street
London E2 6EA
U.K.
Website: www.helixnano.com

Helix Nanotechnologies Inc., founded in 2013, is developing unique DNA-synthesis platforms, with multiple potential applications in life sciences.

One application is a DNA-based molecular tape recorder of drug activity that allows for better screening of drug candidates. This platform provides a one-step assessment of drug efficacy and safety, and overcomes a bottleneck in the present drug-discovery process.

ILLUMINA INC.

5200 Illumina Way
San Diego, CA 92121
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Fax: 858/202-4766
Website: www.illumina.com

Founded in 1998, Illumina Inc. is the global leader in sequencing. Illumina's principle source of revenues includes microarrays and DNA-sequencing products.

Illumina's next-generation sequencing (NGS) platform spans the entire workflow, and the company markets a range of sample preparation and post-sequencing analysis products together with its versatile sequencing platforms.

Illumina's key NGS instrument lines include HiSeq, MiSeq and NextSeq. Illumina's NGS instrument strategy is shown in the table below.

TABLE 117

RECENT PLATFORMS INTRODUCED BY ILLUMINA

Instrument	Targeted Market Segments
MiSeqDx	Reproductive health, HLA typing, CF
HiSeq X Five	Large-scale, whole-genome sequencing
HiSeq 3000	Replace HiSeq 2500 applications
HiSeq 4000	Replace HiSeq 2500 applications
NextSeq 550	Oncology, average risk NIPT, cytogenetics

CF, cystic fibrosis; HLA, human leukocyte antigen; NIPT, noninvasive prenatal test.

Source: BCC Research

Illumina's MiSeqDx, a benchtop sequencing instrument, has strong demand in the human leukocyte antigen typing and CF testing markets.

The HiSeq X Five, made up of five HiSeq X instruments, is designed for customers that do not have the capital to purchase an X Ten system, yet still want to do high-throughput whole-genome sequencing. This system is expected to increase the market for large-scale whole-genome sequencing because it has lower capital costs than the X Ten and uses fewer samples, thus making it easier for customers to use.

The HiSeq 3000 and 4000 instruments both use the patterned flow cell technology that is used on the X Ten system. This represents a significant technical advance over the HiSeq 2500.

The HiSeq 3000 uses a single flow cell, while the HiSeq 4000 uses dual flow cells. Throughput for the HiSeq 4000 is as high as 12 genomes, 100 whole transcriptomes or 180 exomes in 3.5 days. The throughput of the HiSeq 3000 is one-half that of the HiSeq 4000.

The intent of these products is to eventually have companies transition away from the earlier-introduced HiSeq 2500 toward the newer HiSeq 3000 or 4000 platforms. The only case where the HiSeq 2500 would still be used is where longer run lengths are required to be run rapidly.

The NextSeq 550 is a desktop system that combines microarray scanning and sequencing in one platform. The applications are for customers that want to do sequencing and arrays together in the oncology, cytogenetics and prenatal diagnostics industries.

INDUSTRIAL MICROBES INC.

1250 45th Street, Suite 150
Emeryville, CA 94608-2901
Tel: 510/593-8348
Website: www.imicrobes.com

Industrial Microbes Inc., founded in 2015 as a spinout from LS9, engineers yeast that uses methane as a feedstock material. The key advantage of the platform is the use of a cheap feedstock chemical, natural gas, rather than sugar.

The initial target chemical product is malic acid, a starting chemical for making biodegradable plastics.

INGENZA LTD.

Wallace Building
Roslin BioCentre
Midlothian EH25 9PP
U.K.
Tel: 44-131-200-6355
Fax: 44-131-200-6353
Website: www.ingenza.com

Ingenza Ltd., founded in 2003 as a spinout from Edinburgh University, develops and markets synthetic-biology technologies for designing and building microbial production factories.

Ingenza's inABLE platform is a synthetic-biology-based enabling technology for rapid enzyme discovery, expression and process optimization. inABLE allows the construction of multiple genetic constructs within a single reaction, enabling high-throughput screening applications for identifying novel enzyme activity. The platform includes protein design, evolution and synthesis, as well as pathway engineering.

In October 2013, Ingenza formed an alliance with Invista, a producer of polymers and fibers. The alliance included development of platforms for producing bio-derived chemicals. This alliance strengthened Ingenza's capabilities to bring synthetic biology to the market by leveraging Invista's biotechnology and catalysis expertise.

Ingenza, in collaboration with Plymouth University, designed and scaled-up a production process for the antibiotic, epidermicin.

INOVIO PHARMACEUTICALS INC.

660 West Germantown Pike, Suite 100
Plymouth Meeting, PA 19462
Tel: 267/440-4200
Website: www.inovio.com

Inovio Pharmaceuticals Inc., founded in 1979, is a leading immuno-oncology company, and is developing DNA immunotherapies and vaccines together with proprietary electroporation delivery devices. The company uses synthetic-biology platforms for developing its drug candidates.

Inovio uses synthetic biology in its SynCon immune-control strategy whereby it designs antigens and T cells. The company identifies disease-related antigens, encodes a DNA plasmid with genetic codes for each disease-specific antigen and delivers these plasmids into human cells. The modified cells use the genetic codes to produce the encoded disease antigens. The expressed antigens are recognized by the native immune system, which activates antigen-specific T cells and antibodies that eliminate the antigen-expressing cells. The highly optimized DNA plasmids encode the genetic sequence that initiates the specific immune mechanism. These plasmids are produced via synthetic-biology methods.

The SynCon platform is combined with a proprietary electroporation delivery device that is needle free. In April 2016, Inovio acquired Bioject Medical Technologies Inc.'s assets, including its needle-free jet-injection system. This will be combined with Inovio's needle-free electroporation delivery in the expected device for large population vaccine administration.

Inovio has several drug candidates in clinical trials. The lead product candidate is VGX-3100, a cervical dysplasia vaccine that is in Phase III trials. Two product candidates in early-stage development include INO-3112 (combination of VGX-3100 and a DNA-based immune activator) and INO-3112, in Phase I trials for treatment of cervical and head and neck cancer.

Also in Phase I trials are INO-5150 for treating prostate cancer and INO-1400 for treating breast, lung and pancreatic cancer.

Inovio's VGX-3100 vaccine meets an unmet need, as the current HPV vaccines (Merck's Gardasil and Glaxo's Cervarix) do not treat or protect those who are already infected with HPV. This group of women represents a large population. There is no immunotherapy or drug to treat HPV infection, cervical dysplasia or cancer caused by HPV. Thus, VGX-3100 addresses an important need and should be well received if it is eventually approved.

In July 2016, Inovio received notice from Roche that Roche would be discontinuing its existing alliance with Inovio for the development of INO-1800, a DNA immunotherapy against hepatitis B virus. As a result, Inovio retains all rights to the product and will continue to support Phase I studies of INO-1800.

INTEGRATED DNA TECHNOLOGIES INC.

1710 Commercial Park
Coralville, IA 52241
Tel: 800/328-2661
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Website: www.idtdna.com

Integrated DNA Technologies (IDT), founded in 1987 as a spinout from the University of Iowa, is a leading supplier of custom oligonucleotides as well as genomics and molecular-biology tools. IDT is among the top tier of global synthetic DNA suppliers.

In December 2015, IDT acquired the oligonucleotide business of AITbiotech Pte Ltd. (Singapore). The acquisition allowed IDT to expand its synthetic DNA business into the Southeast Asia region.

In June 2016, IDT acquired the South Korean company MBiotech Inc., thus expanding its global sales network within Asia. MBiotech markets and distributes IDT products within South Korea.

In February 2016, IDT formed a partnership with Caribou Biosciences, giving IDT the nonexclusive rights to Caribou's CRISPR/Cas9 reagents for sale on a global basis. The agreement allows IDT to expand its portfolio of CRISPR/Cas9 genome-editing products and offer a complete solution to the customer.

In January 2016, IDT opened a satellite oligonucleotide production facility in San Diego, Calif. This facility is part of IDT's West Coast Operations business, and allows IDT the ability to provide local, next-day services to its oligonucleotide customers on the West Coast.

INTELLIA THERAPEUTICS

130 Brookline Street, Suite 201
Cambridge, MA 02139
Tel: 857/285-6200
Website: www.intelliatx.com

Intellia Therapeutics Inc., founded in 2014, is a gene-editing company that is developing therapeutics using a CRISPR/Cas9 platform.

Intellia's in vivo development programs are focused on liver diseases, and these include transthyretin amyloidosis, alpha-1 antitrypsin deficiency, hepatitis B virus and inborn errors of metabolism. Ex vivo applications in development include CAR-T cell and hematopoietic stem cells (HSCs).

Intellia has a strategic alliance with Novartis for developing ex vivo CRISPR/Cas9 based therapies.

In April 2016, Intellia formed an alliance with Regeneron Pharmaceuticals to develop CRISPR/Cas gene-editing technology for in vivo therapeutics applications. Regeneron has the exclusive right to discovery and develop up to 10 targets, of which five can be nonliver targets.

INTERNATIONAL BUSINESS MACHINES

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Website: www.ibm.com

International Business Machines (IBM), established in 1911, is a global information technology company. IBM's main businesses consist of computer hardware (approximately 14% of sales), services (58%), software (26%) and global financing (2%).

IBM seeks to differentiate its products through innovation and has a large R&D budget to pursue this strategy ($6.3 billion in 2013). IBM supports several synthetic-biology-related projects through this research division.

IBM Research includes a Functional Genomics and Systems Biology Group. IBM Research is working on a DNA transistor and supports other synthetic-biology-related projects.

In 2015, IBM launched its "Watson Genomic Analytics," which combines Watson's cognitive capabilities with human genome data. IBM is doing research to extend this capability in intelligent genomics to the field of synthetic biology.

INTREXON CORP.

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Intrexon Corp., founded in 1998, is developing and marketing a range of synthetic-biology technologies for designing, building and regulating gene programs that control specific cell functions. The main industries that the company is focused on are healthcare, energy, environment and food.

The key synthetic-biology tools that Intrexon has developed include: UltraVector and an associated library of DNA parts (constructing gene programs), RheoSwitch inducible cell switch; Cell Systems Informatics; AttSite Recombinases; Protein Engineering; antibody discovery; LEAP (Laser-Enabled Analysis and Processing for cell identification and selection); and ActoBiotics platform.

UltraVector is a software system for sophisticated DNA construction and computation models for vector design and production of biologic systems. UltraVector can put together genetic programs for efficient assembly of DNA.

RheoSwitch is a gene switch that is activated by a small-molecule ligand. This switch can be used to control the timing, location and level of gene expression and can be used in a wide range of applications in human, animal and plant systems.

Intrexon is unique in its business model, which involves exclusive channel collaborations (ECCs), joint ventures and acquisitions. ECCs allow a partner access to Intrexon's technology in a defined field of use. An example is Intrexon's ECC with Merck-Serono for CAR-T applications.

Downstream synthetic-biology products that Intrexon is pursuing include gasoline additives and next-generation gene therapy products.

For gasoline additives, the focus is on carbon upgrading, or C1 to C4-C15 conversion. The objective is to use engineered bacterial factories to transform C1 chemicals (e.g., methane) to longer chain C4-C15 molecules (e.g., isobutanol). This strategy contrasts with the conventional biofuel strategy of carbon downgrade, that is, producing a C2 molecular (e.g., ethanol) from a C6 (e.g., starch) starting material. The advantage of this strategy is that methane gas is piped easily into the plant and the conversion process generates no solid waste. By contrast, C6 feedstocks must be trucked into a plant and leave residual uncoverted material during processing that must be removed from the plant.

Next-generation gene therapies incorporate synthetic biology innovations such as gene-control systems, which enhance the safety of these therapies. Intrexon's RheoSwitch platform is a competitive advantage in gene therapies for chronic diseases, where gene-expression control is important. Important projects in this field include a joint venture with Sun Pharma (wet age-related macular degeneration), an ECC with Fibrocell (collagen replacement in rare diseases) and an ECC with Agilis (FRDA).

In August 2015, Intrexon acquired Oxitec (U.K.), which is developing synthetic-biology-based methods for controlling pest insects (e.g., moths, mosquitoes, fruit flies and bollworms). The platform, called RIDL (Release of Insects carrying a Dominant Lethal genetic system), employs synthetic parts (sensors, actuators and effectors) that regulate insect function. Insects that are generated with these synthetic parts have offspring that cannot survive in the wild.

The synthetic construct is kept inactivated in insects in the laboratory by feeding them tetracycline. The construct is activated when tetracycline is withheld, and this results in expression of a marker protein, which harms normal insect functions. This process is effective in females only, since the synthetic device is controlled by a sex-specific alternative splicing mechanism.

JOULE UNLIMITED

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Joule Unlimited, founded in 2007, is developing next-generation clean technologies that can convert sunlight and waste carbon dioxide (CO_2) into fuels and chemicals.

The conversion process uses a SolarConverter system, which encompasses the entire process from photon capture to product creation and initial separation. The company has used synthetic-biology tools to create cyanobacteria that can act as a microfactory, and uses carbon from CO2 and sunlight to produce ethanol or alkane (a component of diesel fuel).

The Joule microorganism differs from algae in several important aspects. First, the Joule microorganism is prokaryotic (lack of intracellular organelles, chloroplasts, nucleus and use of prokaryotic ribosomes); second, instead of producing the chemical indirectly (i.e., growing the algal biomass and then harvesting, dewatering and extracting the oil), Joule's microorganism is a catalyst that directly produces and secretes the chemical in a continuous, single-step process; and third, the end product is a liquid hydrocarbon or ethanol rather than a triglyceride (normally produced by algae).

In January 2016, Joule acquired Red Rock Biofuels, a project development company for renewable jet and diesel fuels using biomass feedstocks. Red Rock Biofuels is contracted with FedEx to supply three million gallons of biofuel per year. This will be blended to produce seven million gallons of alternative jet fuel per year from 2017 through 2024. Red Rock will produce the biofuel using wood waste supplied to a sawmill company in Oregon.

JUNO THERAPEUTICS INC.

307 Westlake Avenue North, Suite 300
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Juno Therapeutics Inc., founded in 2013 as FC Therapeutics, is developing cell-based cancer immunotherapies using unique CAR and high-affinity TCR technologies. The company genetically engineers a patient's T cells so that they will recognize and attack cancer cells.

The most advanced therapeutic candidates are JCAR017, JCAR015 and JCAR014. These target the CD19 protein, which is expressed on the surface of most B-cell leukemias and lymphomas.

JCAR017, in Phase I trials, demonstrated the highest cell expansion and longest cell persistence when compared with Juno's other CD19 candidates. These results are expected to lead to improved clinical outcomes.

Juno has several collaborations with pharmaceutical and gene-editing companies, including Celgene Corp., Editas Medicine, Fate Therapeutics, MedImmune and Memorial Sloan Kettering Cancer Center.

The agreement with Celgene is a broad one covering the global development and commercialization of immunotherapies. The collaboration will focus on CAR-T and TCR technologies. Celgene is also an equity investor in Juno.

The alliance with MedImmune combines Juno's CAR-T-cell expertise with MedImmune's checkpoint inhibitor, PDL-1 antibody durvalumab.

LABGENIUS LTD.

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LabGenius Ltd., founded in 2012, offers an online platform for life science researchers to design, analyze and share DNA sequence information.

Genetic construct design is done through an intuitive sequence editor. There is an automatic sequence annotation feature and cloning strategy optimizer.

Analysis of the designed DNA can be done with virtual restriction digests, spot mutation using trace alignment and high-resolution construction maps.

Researchers can manage who sees their sequences with customizable sharing, and they can participate in a community-curated sequence database.

LANZATECH

Illinois Science and Technology Park
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LanzaTech, founded in 2005, is developing bio-derived processes for low-carbon fuels. The company uses synthetic biology to create microbes that catalyze the production of fuels and chemicals from industrial gas resources (gas fermentation microbes).

The company's synthetic-biology platform consists of multiple proprietary genomes, detailed gene-expression database and a plug-and-play gene-expression/gene-regulation system.

In 2015 and 2016, LanzaTech strengthened its business outlook with several alliances for producing bioethanol and isobutene using LanzaTech technology platforms. These alliances included with Aemetis Inc. (for bioethanol), Global Bioenergies (for isobutene) and ArcelorMittal/Primetals Technologies (for bioethanol from steel-making operations).

LATTICE AUTOMATION INC.

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Boston, MA 02215
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www.latticeautomation.com

Lattice Automation Inc., founded in 2013, is developing and marketing synthetic biology software for designing, assemblying and analyzing synthetic-biology constructs.

Lattice's software platform is a tool for planning DNA assembly of large sets of designs and integrates data mining approached for learning rules to optimize genetic networks.

LC SCIENCES

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LC Sciences' platform technology consists of a microfluidic chip that allows for massively parallel synthesis of DNA, RNA or peptides in tiny reaction chambers. This allows production of microarrays with spot densities up to 10 times higher than conventional methods.

LC Sciences manufactures microarrays using this microfluidics technology – called uParaflo – and provides microarray-related services. LC Sciences entered the microRNA (miRNA) expression-profiling service market in 2009 when it launched an miRNA expression-profiling and discovery service using sequencing. Since miRNA expression-profiling services were first launched in the industry in 2006, numerous competitors have entered the market. These include Agilent Technologies (miRNA microarrays) and Applied Biosystems (quantitative RT-PCR assays).

The significance of this technology from a synthetic biology standpoint is that it provides the ability to mass produce synthetic genes or large DNA constructs via multiplexed gene synthesis. In multiplexed gene synthesis, high-purity oligonucleotides are required that can be synthesized in parallel very rapidly. The LC Sciences platform provides oligonucleotides for such applications.

LYGOS INC.

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Lygos Inc., founded in 2012 as a spinout from the University of California at Berkeley's Synthetic Biology Engineering Research Center, is developing synthetic-biology-enabled yeasts and microbes that can manufacture chemicals.

The Lygos platform uses a re-engineered polyketide synthase (multifunctional enzymes) pathway to produce chemicals including nylon precursors, polyester components, styrene and propylene.

In March 2015, Lygos completed its pilot plant operation for producing malonic acid from nonfood, cellulosic sugar feedstocks. The pilot unit was operated at Lawrence Berkeley National Laboratory. In May 2016, Lagos' partner, Sirrus Inc., used Lygos' diethyl malonate (bio-DEM) to produce performance methylene malonates. These products have wide application in a range of industries, including automotive, building and construction, electronics, packaging and hygiene.

MERCK & CO.

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Merck & Co. is a global research-driven pharmaceuticals company. The company is fully integrated in discovery, development, manufacture and marketing of pharmaceutical products. In 2009, Merck and Schering-Plough agreed to merge, creating today's company.

Given its wide product range, including vaccines, Merck has a strategic interest in the development of synthetic-biology research tools. The company has been aggressive in acquiring genomics and synthetic-biology tools to remain strong in its pharmaceuticals business.

In November 2015, Synthace formed an alliance with Merck & Co. to develop advanced biomanufacturing technologies. The alliance will use Synthace's Antha biologic programming language and Merck's expertise in biomanufacturing.

In August 2015, Merck licensed a protein-engineering platform, CodeEvolver, from Codexis. The intent was to develop optimized enzymes that could assist in the production of pharmaceuticals.

METABOLIX INC.

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Metabolix, founded in 1992 as a spinout from the Massachusetts Institute of Technology, is developing and commercializing gene-editing and synthetic-biology-related products and services.

In July 2016, Metabolix went through a corporate restructuring and announced that it decided to focus its business in the agriculture area, with its Yield10 Biosciences division. At the same time, the company announced that it would pursue the sale of its biopolymers business assets.

The restructuring allows Metabolix to focus on developing and commercializing technologies for improving food crops. The initial efforts will be directed toward canola, soybean and corn crops.

In May 2016, Metabolix concluded a license agreement with Tepha Inc. covering Metabolix's polyhydroxy alkanoate biopolymer platform for use in specified medical applications. Tepha is a 2006 spinout from Metabolix.

MICHELIN SA

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Michelin SA develops, produces and sells tires globally. The company has a global network of dealerships and service centers.

Michelin has a collaboration with Amyris to use synthetic biology for producing synthetic rubber for tires. The goal has been to develop a biologic pathway for making renewable isoprene or isoprenol, a key chemical used in automobile tires.

MICROSOFT CORP.

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Microsoft Corp is the world's largest software company, with a very strong position in desktop operating systems and with its Office productivity suite. As a result of its strong market position in these businesses, Microsoft is able to use the resulting cash flow to fund R&D for other markets, including synthetic biology.

Microsoft Research has an interest in synthetic biology for understanding biologic computation. Projects include designing molecular circuits that are made of DNA and programming synthetic biologic devices to perform complex functions.

In April 2016, Microsoft announced that it had purchased 10 million strands of DNA from Twist Bioscience for data-storage applications. The company has tested synthetic DNA and demonstrated that it could encode and recovery 100% of the digital data stored in that DNA. This, combined with DNA's long life (thousands of years) and density (information content is nearly 1 million gigabytes per gram of DNA), have encouraged Microsoft to continue development of this application.

MODULAR GENETICS INC.

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Modular Genetics Inc. is developing an automated gene-engineering platform, CombiGenix, that allows customers to synthesize, modify and recombine genes to create novel DNA molecules. This platform can be combined with protein-design tools and high-throughput screening to become an automated platform for protein evolution.

The main markets for which this platform is immediately being used for include protein therapeutics and natural-product-based drugs.

For the personal-care market, the company demonstrated production of acyl glutamate under a U.S. National Science Foundation grant. Under this project, Modular Genetics was able to produce and purify the surfactant, which was shipped to Unilever. Unilever confirmed the identity of the compound and that it was of high purity.

MORPHOSYS AG

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MorphoSys AG, founded in 1992, is developing a proprietary pipeline of therapeutic antibodies using its synthetic-biology-based antibody development platform. The company has collaborations with several major pharmaceutical companies (e.g., GlaxoSmithKline, Celgene and Novartis) and uses the profits from these to fund its own pipeline.

The company has developed a large library of human antibodies, which it has used to start 89 partnered discovery programs (21 are in the clinic) with other pharmaceutical companies. In addition, MorphoSys has 14 in-house proprietary programs (six are in preclinic or clinic).

In October 2010, MorphoSys acquired Sloning BioTechnology, a synthetic-biology tool company. The rationale for the acquisition was to incorporate the synthetic-biology platform, Slonomics, into MorphoSys' existing antibody drug development program as well as for developing new therapeutics and diagnostics. The pharmaceutical industry is working to increase its R&D productivity and develop better drugs, including biologics, which can compete better with generics. MorphoSys' acquisition of Sloning's synthetic-biology platform gives it more leverage to benefit from these industry trends.

Sloning's platform uses synthetic DNA triplet building blocks to create diverse protein libraries that have amino acids in precise, predetermined positions. The technology provides a significant competitive advantage by optimizing the affinity, stability, solubility and immunogenicity of antibodies in one step. This reduces the time in the antibody discovery process by up to 33%, potentially allowing a candidate to reach the clinical stage in less than three years.

Since its acquisition of Sloning, MorphoSys has created Ylanthia, a large antibody Fab library. Ylanthia can be screened in vitro to identify antibodies (Fab format) that bind the target molecules with high affinity. After this screening, antibody development and optimization is performed using the Slonomics and asYla platform.

MYRIANT TECHNOLOGIES LLC

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Myriant Technologies LLC, established in 2009 as a spinout from BioEnergy International, is developing bioprocesses for a range of specialty chemicals that can compete directly with petroleum-based chemicals. Myriant's product portfolio includes biosuccinic acid as well as acrylic acid, lactic acid, muconic, acid and fumaric acid.

From its biosuccinic acid, Myriant is developing Myrifilm Zero-VOC Coalescing Solvent, which is used to manufacture renewable coatings and adhesives.

Myriant's technology platform includes biomass pretreatment, genetic engineering, fermentation, separation and purifications and refinery scale-up. Myriant uses synthetic-biology techniques, including metabolic engineering and directed evolution, to modify E. coli bacterium, yeast, thermophiles and other microbes through the chromosome rather than the cell wall. This results in an organism that is more stable upon commercial production.

NEW ENGLAND BIOLABS

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New England Biolabs (NEB) is a leading supplier of reagents for the life science industry. Products include genomics, proteomics and drug-discovery reagents and kits. The company is a specialist and leader in the supply of restriction enzymes.

NEB markets several synthetic-biology tools to the life science industry, including BioBrick Assembly Kits, Gibson Assembly Cloning Kits, NEBCloner and Golden Gate Assembly Tool.

In April 2009, NEB launched the BioBrick Assembly Kit, which was developed jointly with Ginkgo Bioworks. BioBricks are DNA fragments that encode proteins, promoters and ribosome binding sites, among others. These parts have been standardized and are contained in a registry of plasmids, whose coding sequences are flanked by identical restriction sites. The standardized flanking sites are used to ligate the parts in any order to create novel constructs.

The kit allows synthetic biologists to assemble BioBrick parts into multicomponent genetic systems. The BioBrick parts are DNA sequences that encode a biologic function and can be easily combined with another BioBrick part.

The launch of the BioBrick Assembly Kit was a first in synthetic biology – it was the first commercial product to support an open standard in synthetic biology. The kit is offered exclusively by NEB.

In February 2012, NEB and Synthetic Genomics (through its SGI-DNA subsidiary) formed a partnership to launch the Gibson Assembly Cloning kit and NEBuilder Primer Design tool.

Gibson Assembly allows for the fast assembly of many DNA fragments in a one-step, isothermal process. It is used by synthetic biologists to manipulate DNA and assemble it into large constructs.

NEB provides products that support CRISPR genome-editing applications. These tools include EnGen mutation detection kits, EnGen Cas9 Nuclease kits (for in vitro cleavage of dsDNA), site-directed Mutagenesis kits (for insertion of target sequence into Cas0-agRNA constructs) and HiScribe RNA synthesis kits (for generating single-guide RNA and Cas9 mRNA).

NOVARTIS PHARMA AG

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Novartis AG, formed in 1996 through a merger of Ciba-Geigy and Sandoz, is one of the world's leading pharmaceutical companies. The company's main businesses are prescription pharmaceuticals (56% of total sales in 2014), Alcon vision care products (18%), Sandoz generic drugs (16%), vaccines and diagnostics (3%) and consumer health products (7%).

In 2014, Novartis acquired the oncology business of GlaxoSmithKline, significantly strengthening its global position in oncology drugs.

In January 2015, Novartis formed a partnership with Intellia Therapeutics in the field of genome editing. The objective was to develop new CAR-T-cell therapies using Intellia's CRISPR/Cas9 platforms. Novartis is using these tools to engineer T cells that retain specific edits longer (by inserting several copies of edits across the genome). In addition, the collaboration allowed for use of CRISPR/Cas9 editing on HSCs, the precursors of adult T cells. Initial applications for these programs included sickle cell disease and other blood disorders.

The Novartis Institutes for BioMedical Research (NIBR) is closely involved in using synthetic-biology tools for medical applications. NIBR collaborates with Caribou Biosciences and Intellia Therapeutics in genome-editing technologies.

In January 2015, Novartis licensed the CRISPR technology platform from Caribou Biosciences and is using this as a research tool in NIBR to edit genetic loci of mice and of cultured cells.

In May 2016, Novartis formed an alliance with the Broad Institute and the University of California, San Francisco, to use synthetic biology and informatics tools to predict the chemical structures of compounds derived from microbiomes. With the initiative, called Novartis-Foundry Sequence-to-Molecule Pipeline, the group seeks to discover new classes of natural pharmaceuticals. The strategic approach is (1) to predict the many thousands of chemical structures that microbiomes can product, (2) to evaluate how these molecules affect physiology and behavior and (3) to develop insights that will lead to new pharmaceutical classes.

NIBR has an alliance with Surface Oncology covering next-generation immuno-oncology applications.

NOVOZYMES A/S

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Novozymes A/S is the world's largest producer of industrial enzymes, with an estimated global market share of 48%. The company's 2015 sales are divided roughly as follows: household detergents (33% of revenues); food and beverages (27%); bioenergy (18%); agriculture (15%); and pharmaceuticals (7%).

Novozymes is using synthetic-biology methods to develop new enzymes and enzyme cocktails.

Novozymes is a key supplier of enzymes to the biofuels industry and has a leading market share in enzymes to the bioethanol industry. The company uses DNA-sequencing technologies and bioinformatics as enabling technologies for its enzyme-development programs.

OMEGA BIO-TEK INC.

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Omega Bio-Tek Inc., founded in 1998, supplies nucleic acid purification products to the life sciences industry. Products include plasmid, genomic DNA and RNA isolation kits, as well as DNA and RNA clean-up, electrophoresis and PCR reagents.

Omega also synthesizes genes and long DNA constructs, optimizes codon usage and delivers these products in cloned vectors. DNA sequences of up to 5,000 bp are synthesized. The company is a second-tier supplier of synthetic genes, with a primary corporate focus on nucleic acid purification technologies.

ORAGENICS INC.

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Oragenics Inc., founded in 1996, is developing and marketing probiotic and lantibiotic products. The company markets four oral probiotic products, which are sold under the Evora brand.

In June 2012, Oragenics began an exclusive collaboration with the synthetic-biology company Intrexon to develop broad-spectrum lantibiotic therapeutics for the drug-resistant antibiotic market. Under that agreement, Intrexon performs most of the discovery and cell-engineering development, and Oragenics conducts preclinical and clinical trials of candidate lantibiotics.

Lantibiotics are peptides that have a broad spectrum of activity against infectious agents including *Streptococcus pneumoniae*, multidrug-resistant *Staphylococcus aureus* (MRSA), *Mycobacterium tuberculosis* and *Clostridium difficile*. Oragenics' lead lantibiotic compound is OG253, for treating *C. difficile* infection in enteritis.

The Intrexon synthetic-biology technology is being used to develop a commercial synthesis approach for its drug compounds. Intrexon's approach involves extracting genes responsible for lantibiotic production from bacteria cells, modifying and inserting these genes into mammalian or yeast cells and producing lantibiotics through fermentation.

ORIGENE TECHNOLOGIES INC.

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Origene Technologies Inc. is a research tool company that developed a large collection of full-length human complementary DNAs (cDNAs) in a standard expression vector. The company provides genome-wide research tools and technology platforms for life science research and drug-discovery applications.

In August 2010, Origene acquired the synthetic-biology company Blue Heron Biotechnology. The acquisition strengthened Origene's research tools business by bringing together Origene's large set of human cDNA clones with Blue Heron's gene-synthesis capabilities.

Blue Heron, which operates as a wholly owned subsidiary of Origene, produces synthetic genes using a proprietary production platform, GeneMaker. GeneMaker is a proprietary high-throughput platform for design and synthesis of DNA sequences. Blue Heron also relies on proprietary gene-design software to differentiate itself in this market and access the value-added synthetic-gene segment. The software allows the company to optimally construct a large, complex gene, fragment by fragment.

Origene offers CRISPR/Cas9 genome-editing systems for the synthetic-biology research market.

PACIFIC BIOSCIENCES OF CALIFORNIA INC.

1380 Willow Road
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Website: www.pacificbiosciences.com

Founded in 2001, Pacific Biosciences of California Inc. (PacBio) is developing and commercializing third-generation, single-molecule sequencing technology. RS, the company's first sequencing instrument, was introduced in early 2011.

PacBio's technology platform, originally licensed from the Cornell Nanobiotechnology Center, uses DNA polymerases anchored in 70-nanometer wells (i.e., zero-mode waveguides) to incorporate nucleotides in real time. DNA molecules are trapped in these small wells, which are fabricated on thin sheets of metal. Inside each well, the dsDNA dissociates into single-stranded DNA (ssDNA). The DNA polymerase uses ssDNA as a template to synthesize a complementary strand, incorporating nucleotides with fluorescent tags at the gamma-phosphate position. A digital camera observes the process in real time, and its images determine the order of the bases that are added.

As with other DNA polymerase-dependent sequencing methods, read lengths, which are functions of the polymerase lifetime, can be 1,200 to 1,500 bases. The density of the wells determines the sequencing throughput.

An advantage of this technology approach is that it avoids fragmenting the DNA into short sequences and then reassembling them into a full genome. A second advantage is low reagent use for driving the nucleotide incorporation process.

The two key aspects of PacBio's technology platform are fluorescent labels at the gamma-phosphate position of the nucleotide and zero-mode nanowells.

Incorporating the fluorescent label at the gamma-phosphate position allows the label to be cleaved off following each base incorporation cycle, giving a readily extendable, natural DNA strand for the next cycle. This means that the DNA polymerase can operate at its natural speed and efficiency, which is the key to achieving long reads. Pacific Biosciences recently strengthened its position in gamma-phosphate labeling with the acquisition of LI-COR's technology portfolio in this area.

The zero-mode nanowell provides a reaction chamber for the rapid incorporation of each nucleotide while allowing optical detection of each base by the waveguide structure at the bottom of the well.

The main advantages of PacBio's platform are fast turnaround times, long read lengths and kinetic analysis. Fast turnaround times (i.e., 45 minutes versus eight days for some other procedures) may be valuable for infectious disease monitoring, in which rapid turnaround is critical for outbreaks. Long read lengths may allow for the sequencing of DNA, which is more difficult to do with shorter read lengths. Kinetic analysis (i.e., determining the length of time it takes to incorporate the base by the polymerase) may allow for epigenetic analysis.

PacBio has commercial alliances with four sequence-capture companies: Agilent Technologies, Fluidigm, RainDance Technologies and NuGen. The company is pursuing this strategy to cover all applications for its sequencing platform because each sequence-capture technology has its advantages and limitations. The market for NGS is still emerging, so not all applications are known. Thus, partnering with four different sample preparation companies provides great flexibility in meeting emerging applications needs, from whole-exome to targeted-gene resequencing.

PacBio markets the PacBio RS II genetic analyzer, as well as consumable products including sealed and packaged SMRT Cells, reagent kits, such as template preparation, binding and sequencing kits.

PFIZER INC.

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Pfizer Inc. is a global research-driven pharmaceutical firm that is fully integrated into research, development, manufacturing and marketing of drugs. Pfizer has an exceptional breadth and depth of products in the drug market. Major products include Lyrica (nerve pain and epileptic seizures), Prevnar/Prevnar 13 vaccines, Enbrel (plaque psoriasis and rheumatoid arthritis) and Celebrex (arthritis and pain).

Pfizer has used a strategy of acquiring large pharma companies to achieve long-term growth. The company acquired Warner–Lambert in 2000, Pharmacia Corp. in 2003 and Wyeth in 2009. This strategy is unlike competitors Merck or Roche, which have targeted strategic biotech acquisitions that are small-to-mid sized and provide genomics or proteomics tools.

In October 2009, Pfizer and Wyeth Pharmaceuticals announced a deal where Wyeth was acquired for approximately $68 billion. Wyeth has a strong biologics platform and presence in vaccines, with significant animal health and consumer product businesses. Wyeth has a strong research focus on several areas where Pfizer sees opportunity, including Alzheimer’s disease, oncology and central nervous system (CNS) disorders.

As the world’s leading pharmaceutical company, Pfizer is active in the use of synthetic-biology tools to address problems in cell and protein biotherapeutics. In its Research Technology Center (Cambridge, Mass.), Pfizer is attempting to improve the performance of biotherapeutics by producing novel systems that combine different components of biologic systems in novel ways.
Specific interests of Pfizer’s research in synthetic biology include next-generation microbial and mammalian production systems and next-generation process and manufacturing technologies.

To assist its position in the immune oncology market, Pfizer in-licensed Merck KGaA’s PD-L1 inhibitor, avelumab, in 2014. Pfizer also has an in-house PD-1 inhibitor, OX40, 4-1BB

and CCR2. Pfizer's IO franchise is relatively early stage, and the company views this market as a long-term opportunity.

PHYLOGICA LIMITED

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Phylogica Limited, founded in 2001 as a spinout from the Telethon Institute for Child Health Research and the Fox Chase Cancer Center, is developing a drug-discovery platform based on proprietary Phylomer peptides. Phylomer libraries contain more than 400 billion unique natural peptides, which have stable drug-like structures.

Phylogica uses synthetic-biology tools to discover novel peptides as part of its Phylomer libraries. These libraries can be used to create novel peptide drugs and to validate new drug targets. Peptides are important as drug candidates because they can modulate intracellular protein to protein interactions. Peptides are the right size for these applications because, unlike small molecules, peptides are large enough to interact with proteins, and, unlike antibodies, peptides are small enough to easily enter the cell.

Phylogica has partnerships with Pfizer (2010, for novel peptide vaccines), Medimmune (2010, for discovery of antibiotics against hospital-acquired infections) and Roche (2009, for discovery of cell-penetrating peptides against CNS disease).

In January 2012, Phylogica formed a partnership with Janssen, to use Phylomer libraries for discovering new cell-penetrating peptides.

PHYTOWELT GREEN TECHNOLOGIES GMBH

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Phytowelt GmbH, founded in 2006 from a merger of Phytowelt GmbH and GreenTec GmbH (a spinout from the Max-Planck-Institute for Plant Breeding Research), is developing tools and products for using plants in industrial production processes. Among its products are plant-based production organisms for synthetic-biology applications.

Phytowelt specializes in contract research for optimizing plants and enzymes for biosynthesis processes.

PRECISION BIOSCIENCES

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Precision BioSciences is a genome-editing company commercializing the use of a MegaNuclease technology called ARCUS. ARCUS genome editing is based on homing endonucleases, which are site-specific DNA cutting enzymes. These nucleases can recognize DNA sequences up to 40 bp in length and then introduce a double-stranded break at the recognition site.

The ARCUS platform uses a synthetic enzyme that is very similar to a homing endonuclease and that has been modified to make it easy to customize for gene editing.

The main feature of ARCUS is that it has very good site specificity and the endonuclease is small in size (310 amino acids). High specificity means that random, off-target effects can be minimized. The small size allows the endonuclease to be delivered by a range of strategies.

In February 2015, Precision BioSciences formed a collaboration with Baxalta Inc. covering the use of genome-editing tools in immuno-oncology applications. Baxalta will use genome-editing tools to develop allogeneic CAR-T-cell therapies for cancer applications. The companies will develop CAR-T therapies for up to six targets, with a target clinical trials date of late 2017. Precision BioSciences will perform early-stage research, and Baxalta has the exclusive right for late-stage development and commercialization.

The main medical applications for which Precision BioSciences is developing its technology include immuno-oncology and genetic diseases. The company is also developing genome-editing technologies for agricultural seed improvements.

PROKARIUM HOLDINGS LTD.

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U.K.
Tel: 44-781-136-7729
Website: www.prokarium.com

Prokarium Holdings Ltd. is using synthetic-biology tools to engineer immune-cell-targeting bacteria that express vaccines from within the human body. The bacterium that has been modified is salmonella. The engineered bacterium enters the body through the gut lining; immune cells then engulf the bacterium inducing it to produce vaccine.

The oral vaccine platform, Vaxonella, can deliver most types of protein vaccines. Infectious disease vaccines in preclinical development include chlamydia and *C. difficile*. A typhella vaccine is in discovery/research stage of development.

The advantages of this approach are (1) oral delivery and (2) the vaccine is thermally stable at 37°C for many weeks.

QTEROS INC.

99 Pulpit Hill Road
Amherst, MA 01002
Tel: 413/531-6884
Website: www.qteros.com

Qteros (formerly Sunethanol) is developing a cellulosic ethanol production platform based on its Q Microbe (Clostridium phytofermentans) technology platform. This microbe can digest cellulosic biomass and convert the resulting sugars to ethanol in a one-step process, thus eliminating the conventional multistep process.

The Q Microbe has been genetically optimized by synthetic-biology techniques to maximize the conversion of biomass into ethanol.

RADIANT GENOMICS INC.

1250 45th Street, Suite 150
Emeryville, CA 94608
Tel: 510/621-7332
Website: www.radiantgenomics.com

Radiant Genomics Inc. is developing a synthetic-biology-enabled natural-product (e.g., ketides, peptides) drug-discovery platform.

Radiant Genomics is using synthetic-biology tools to engineer bacterial genera that produce complex secondary metabolites including polyketides and nonribosomal peptides. These bacteria can thus produce metabolites that are encoded in cryptic gene clusters, generating a high diversity of novel products.

In February 2015, Radiant Genomics formed a collaboration with Dow AgroSciences to develop natural products for crop protection applications. As a result of this collaboration, Dow gained access to Radiant’s synthetic-biology-based natural-products-discovery platforms.

RENNOVIA INC.

3040 Oakmead Village Drive
Santa Clara, CA 95051
Tel: 408/855-6450
Fax: 408/855-6451
Website: www.rennovia.com

Rennovia, founded in 2009, is using a proprietary catalyst platform to produce glucaric acid, adipic acid (ADA), 1,6-hexanediol, and hexamethylenediamine.

The company's technology platform includes advanced biocatalysts for converting renewable feedstocks to specialty chemicals. Rennovia also employs high-throughput screening methods for synthesis and screening of biocatalysts.

In March 2014, Rennovia partnered with Johnson Matthey to develop catalysts for producing glucaric acid and ADA. Johnson Matthey's Davy Technologies contributes the engineering and construction capabilities for the plant.

In July 2015, Rennovia and Johnson Matthey announced that they had successfully started-up the mini-plant for producing glucaric acid from glucose. The mini-plant is also capable of producing ADA.

In May 2016, Rennovia formed an alliance with Stora Enso in which the partners will use Rennovia's high-throughput catalyst-discovery platform to develop new processes for several chemicals of interest to Stora Enso. Stora Enso markets pulp grades to the paper, board and tissue industries.

ROOSTERBIO INC.

4539 Metropolitan Court
Frederick, MD 21704
Tel: 301/360-3545
Website: www.roosterbio.com

RoosterBio Inc. manufactures and markets standardized stem cell products for the life sciences industry. A key bioprinting product is cellular bio-ink, which is composed of adult human mesenchymal stem cells (hMSCs). MSCs are a versatile type of stem cell and important in regenerative medicine because they can differentiate into a wide range of cell types.

RoosterBio markets three main products: cells (sold in vials); growth media specific for hMSCs; and screening kits for multiple hMSC donors and bundles (combine cell and media systems).

RoosterBio has an alliance with CellInk covering the use of hMSC-based bio-inks. The objective is to offer easy to print stem cell bioprinting technologies to the market.

The goal of RoosterBio is to re-engineer a patient's cells so that new organs can be synthetically designed by the cell in a laboratory and then transplanted into the patient's body.

ROYAL DSM NV

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6411 TE Heerlen
The Netherlands
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Fax: 31-45-578-8111
Website: www.dsm.com

Royal DSM NV (formerly Dutch State Mines) is a major producer of basic chemicals. DSM Pharma is a division of DSM that provides fermentation manufacturing services to the pharmaceutical and biopharmaceutical industries. A key core competency of DSM is fermentation. The company provides custom contract manufacturing services for different cell production systems, processing techniques and product types.

Important synthetic-biology tools offered by DSM include strain development, strain production and enzymatic modification.

Several products have resulted from the synthetic-biology tools that DSM developed.

In 2006, DSM commercialized cephalexin, a synthetic antibiotic, using a penicillin-producing microbial strain that uses a three-step process and saved 11 chemical steps over the older chemical process. DSM engineered two enzyme-encoding genes to give a one-step direct fermentation of adipoyl-7-ADCA, which is then converted to cephalexin by two enzymatic steps.

In June 2010, DSM formed a joint venture company, Reverdia, with Roquette Freres. Reverdia is commercializing and marketing Biosuccinium, a biosuccinic acid product

The market for this product is estimated to be 500,000 tonnes per year by 2020. Applications for biosuccinic acid include renewable thermoplastics (polybutylene succinate), solvents, BDO/tetrahydrofuran, food, freezing-point depression agents, plasticizers, polyurethanes, coatings and pigments, pyrrolidones and pharmaceuticals.

The commercial-scale succinic acid plant, located in Cassano Spinola, Italy, was completed in December 2012, and has a capacity of 10,000 tonnes per year.

In October 2014, Reverdia began licensing Biosuccinium to companies interested in integrating this product into their bio-based materials.

DSM and its partner, Poet, operate a plant in Emmetsburg, Iowa, that has a production capacity of 20 million gallons of cellulosic ethanol per year. The feedstock for this plant is baled corn cobs, leaves, husk and stalk.

SAMPLE6 TECHNOLOGIES

840 Memorial Drive, 4th Floor
Cambridge, MA 02139
Tel: 617/393-7600
Website: www.sample6.com

Sample6 Technologies is developing near real-time microbial diagnostics by using synthetic-biology tools to modify bacteriophages.

The company is developing diagnostics that can be applied in the food-detection area. The diagnostics target bacteria such as E. coli, salmonella or listeria, which can cause illness.

The food industry performs active testing today for these pathogens; the current testing methods using PCR require up to two to three days, so the food that does get shipped sometimes needs to get recalled or has the potential to make the consumer sick. The Sample6 test provides results within two to three hours, significantly shortening the time to answer.

Sample6's lead products are Detect/L (to identify listeria contamination) and Sample6 Control (software for food safety programs). Sample6 has performed genome engineering on a bacteriophage so that it specifically targets and infects listeria and then causes the bacterium to produce luciferase, thus providing a useful detection method. The Detect/L test does not require any DNA amplification and can be done in real time. Detect/L is approved by the USDA and AOAC and detects listeria monocytogenes.

Additional products in development include for detection of salmonella and E. coli 0157.

SANGAMO THERAPEUTICS INC.

501 Canal Boulevard
Richmond, CA 94804
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Website: www.sangamo.com

Sangamo Therapeutics Inc., founded in 1995, develops and markets unique transcription factors (DNA binding domains, specifically zinc finger proteins [ZFPs]) capable of targeting and regulating genes anywhere in the genome. This capability to regulate gene function is useful in synthetic-biology technologies.

Zinc finger DNA-binding proteins can be very specific and engineered to either improve the expression of useful genes or reduce the expression of harmful genes. Sangamo is a leader in zinc finger applications including therapeutics and as an enabling tool for synthetic biology. In therapeutics, Sangamo is developing a new class of drugs using modified zinc DNA binding proteins to regulate and modify disease-related genes.

Sangamo's lead ZFP drug candidate is SB-728-T, for treatment of HIV/AIDS. This drug is in Phase II and Phase I/II clinical trials. In addition, Sangamo is involved in ZFP-based clinical studies for hemophilia B and MPS1 (lysosomal storage disorder [LSD]) and preclinical

programs in hemophilia A and other LSDs. In February 2016, the FDA cleared the investigational new drug application for the MPS1 product.

Sangamo is partnered with Biogen Inc. to develop and commercialize ZFP drugs for hemoglobinopathies and with Shire International GmbH for Huntington's disease.

SANOFI-AVENTIS

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France
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Website: www.en.sanofi-aventis.com

Sanofi-Aventis develops and manufactures pharmaceuticals. Primary markets include cardiovascular, oncology, CNS and internal medicine formulations. The company is the third-largest pharmaceutical company in the world as measured by revenues. Sanofi-Aventis has one of the largest R&D budgets in the world. It has a very strong market share in Europe, and sales in the U.S. are growing.

While Sanofi has world-leading franchises in cardiovascular and diabetes, it also has a very strong vaccine business and is focused on alleviating developing world diseases including malaria, West Nile virus and dengue fever.

Sanofi obtained the rights from the synthetic-biology company, Amyris, to scale-up the semisynthetic drug intermediate, artemisinin, which is used to treat malaria.

In April 2013, Sanofi started up a semisynthetic artemisinin plant in Garessio, Italy. The plant was based on the Amyris process. Due to several market factors, Sanofi sold this plant to Huvepharma in 2016.

SCARAB GENOMICS LLC

1202 Ann Street
Madison, WI 53713
Tel: 608/257-1624
Fax: 608/257-2043
Website: www.scarabgenomics.com

Scarab Genomics LLC, founded in 2002 as a spinout from the University of Wisconsin, is developing and commercializing minimal genomes based on synthetic-biology tools.

Scarab's technology platform, called Clean Genome, is based on the organism E. coli, a very useful microorganism for life science industries. The company has created a version of E. coli, K-12, in which more than 15% of its genome has been deleted. The deleted DNA includes nonessential genes, insertion sequence elements, recombinogenic or mobile DNA, cryptic viruses and virulence genes. This synthetically engineered strain of E. coli is very useful as a cellular factory with improved genetic stability and metabolic efficiency.

The main advantage of the E. coli strain developed by Scarab is that, with the nonessential genes and DNA removed from the genome, both its function and genetic stability are improved. Functionally, protein synthesis and electroporation efficiency is significantly better than the wild-type version. This makes it possible to clone some genes that otherwise would not be able to be cloned.

IP held by the company includes an exclusive license from the University of Wisconsin to US 6989265, which claims a minimal E. coli genome and any synthetic cell derived from the E. coli genome.

The main products using the Clean Genome platform include media, chemically competent cells, electrocompetent cells, strain identification kits, vectors and electroporation accessories.

SEA6 ENERGY PVT LTD.

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Bellary Road, GKVK Post
Bangalore 560065
India
Tel: 91-80-6718-5225
Website: sea6energy.com

Sea6 Energy, a spinout from IIT Madras (India), is using synthetic biology to produce biofuels, plastics, food additives and so forth from microalgae and seaweed.

Sea6 Energy’s main products are biostimulants, Tarma and Spurt, which can be sprayed onto plants to aid in growth.

Sea6 Energy has an alliance with Novozymes to develop technology for producing ethanol, fine chemicals and proteins from seaweed. The companies are using enzymes to convert seaweed-based carbohydrates to sugar, which can then be fermented to produce ethanol, fine chemicals, food proteins and plant fertilizers.

SGI-DNA INC.

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La Jolla, CA 92037
Tel: 855/474-4362
Fax: 858/777-5694
Website: www.sgidna.com

SGI-DNA Inc., founded in 2013 as a wholly owned subsidiary of Synthetic Genomics Inc., is developing and commercializing DNA-synthesis technologies and services for the life science industries.

The company produces synthetic genes, genetic pathways, chromosomes and whole genomes. It also markets synthetic biology reagents based on its Gibson Assembly DNA

cloning platform. Gibson Assembly was used to create the first fully synthetic cell in 2010 and is used widely in synthetic biology laboratories.

SGI's synthetic biology reagents include HiFi 1-Step, Ultra and Site-Directed Mutagenesis kits for DNA construct assembly.

In January 2016, SGI launched its Cell Engineering Services business, which allows life science researchers to optimize their mammalian cell engineering. This service uses SGI's synthetic biology capabilities to create complex multigenic DNA constructs to meet a wide range of needs in the research community.

In July 2016, SGI-DNA reached an agreement with VWR, giving VWR exclusive rights to distribute SGI's synthetic biology reagents in North America and Europe.

SHANGHAI GENERAY BIOTECH CO. LTD.

13–14 Building, No. 5398 Shenzhuan Road
Songjiang District
Shanghai 201619, China
Tel: 86-400-026-8886
Fax: 86-21-6784-0416
Website: www.generay.com.cn

Shanghai Generay Biotech Co. Ltd. supplies synthetic genes using PCR-based technologies. In addition, the company provides oligonucleotide synthesis, sequencing and molecular-biology reagents to the life science industry in China.

Generay is a leading supplier of synthetic genes in China. The company has several patents on oligonucleotide, gene synthesis and single nucleotide polymorphism genotyping.

In addition to oligonucleotide and gene synthesis, Generay supplies molecular-biology kits and has more than 30 distributors in China as well as distributors in North America, Europe and Southeast Asia.

SHANGHAI SHINEGENE MOLECULAR BIO-TECHNOLOGIES INC.

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Minhang District
Shanghai 201109
China
Tel: 86-21-54460832
Fax: 86-21-54460831-13
Website: www.shinegene.org.cn

Shanghai ShineGene, founded in 2003, provides a range of DNA, protein and peptide synthesis services and products. The company supplies synthetic genes using a PCR-based technology.

The gene-synthesis service is done on a custom basis, with quick turnaround and high accuracy being the major selling points.

SIGMA ALDRICH CORP.

3050 Spruce Street
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Fax: 314/771-5757
Website: www.sigmaaldrich.com

Sigma Aldrich Corp., a subsidiary of Merck KGaA since November 2015, is one of the world's largest suppliers of chromatography products, research chemicals, reagents and related products. The company markets more than 170,000 chemical products, under the Sigma, Aldrich, Fluka and Supelco brand names.

More than 75% of sales are to life science customers, with the remaining 25% to high technology customers.
The Research business unit markets many of the genomic, proteomic and other life science research products, including synthetic-biology products.

Sigma Aldrich participates in the synthetic-biology market in several ways, as described below.

Sigma–Genosys, a wholly owned subsidiary of Sigma Aldrich, is a leading supplier of custom oligonucleotides, gene arrays, and synthetic peptides.

Sangamo Therapeutics is collaborating with Sigma Aldrich on the use of nontherapeutic applications of its technology.

In November 2015, Sigma Aldrich formed an alliance with Genewiz and Oxford Genetics covering the use of web-based ordering systems for gene synthesis. Genewiz is a contract research organization that offers DNA-sequencing and DNA-synthesis services. Oxford Genetics markets SnapFast, a line of modular plasmids and expression systems. The alliance will allow researchers to instantaneously get quotes for genes of up to 5 kb and use the SnapFast vectors without any licensing fees. It is hoped that these factors will increase the use of synthetic genes by researchers and smaller biotechnology companies.

SILICOLIFE LDA.

Rua do Canastreiro, 15
4715-387 Braga
Portugal
Tel: 351-253-070-273
Fax: 351-965-221-885
Website: www.silicolife.com

SilicoLife is developing and marketing informatic tools for biotechnology applications, including for building cell factories.

SilicoLife developed its Platform for Metabolic Engineering, which combines the in silico design of microbial cell factories with wet laboratory validation.

The main services that the company offers includes construction and validation of cell factory models, custom software development, and analysis and integration of experimental genomic data.

SOLIGENIX INC.

29 Emmons Drive, Suite C-10
Princeton, NJ 08540
Tel: 609/538-8200
Fax: 609/452-6467
Website: www.soligenix.com

Soligenix Inc. is developing products to treat life-threatening side effects of cancer treatments and serious gastrointestinal diseases, as well as vaccines for bioterrorism agents.

In May 2013, Soligenix began collaborating with Intrexon Corp. on the use of synthetic-biology tools to develop a therapy for melioidosis.

Melioidosis is caused by Burkholderia pseudomallei, a bacterium that is a high-priority biodefense threat and can be spread by aerosol. The B. pseudomallei bacterium is highly resistant to antibiotic treatments and is endemic in Southeast Asia and Northern Australia.

In the collaboration, Intrexon will perform discovery and development of antibody drug candidates and produce monoclonal antibodies (mAbs) targeting melioidosis. Soligenix will perform preclinical and clinical development, regulatory interface and commercialization.

In May 2016, the FDA granted fast-track designation for SGX943 for treating melioidosis. SGX943 is a synthetic peptide that has a novel mechanism of action because it is both anti-inflammatory and anti-infective.

SPIBER INC.

234-1 Mizukami
Kakuganji Tsuroka
Yamagata 997-0052
Japan
Tel: 81-2-3525-3907
Website: www.spiber.jp

Spiber Inc., founded in 2014, is using synthetic-biology technologies to create protein-based materials for a range of applications.

The initial target market for these new materials is outdoor apparel, chosen because of its rapid adoption cycle and need for high-performance materials. Spiber is partnered with The North Face, and introduced its spider-fibroin-based protein material, Qmonos, in 2016.

The initial product is an outerwear jacket, Moon Parka, which is designed to withstand the conditions of the South Pole. The jacket is the first piece of clothing that is made from synthetic protein material.

SYNLOGIC

200 Sidney Street #320
Cambridge, MA 02139
Tel: 617/401-9975
Website: www.synlogictx.com

Synlogic is developing platforms in the emerging synthetic-biology discipline of synthetic biotics. In synthetic biotics, medicines with origins in natural probiotic bacteria are genomically programmed to provide therapeutic benefits.

Specifically, genetic circuits are engineered into bacteria, allowing them to sense a patient's internal environment and respond by switching a metabolic pathway on or off. When the pathway is switched on, the metabolic pathway to achieve therapeutic effect is activated.

Two lead synthetic biotic therapies are for treating the rare genetic disorders urea cycle disorder and phenylketonuria (PKU).

In February 2016, Synlogic formed an alliance with AbbVie covering the development of synthetic biotic medicines for treating inflammatory bowel disease. The emphasis will be on Crohn's disease and ulcerative colitis. The partnership combines Synlogic's synthetic biology and microbiome platforms with AbbVie's expertise in metabolic and inflammatory diseases.

SYNPROMICS LTD.

9 Little France Road
Edinburgh EH16 4UX
U.K.
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Fax: 44-131-658-5302
Website: www.synpromics.com

Synpromics, founded in 2010, is developing synthetic promoters (i.e., man-made gene regulators) that can be used to control genes under a range of conditions. The target market areas for this technology include research tools, diagnostics and gene therapeutics.

The company's IP relates to the mechanisms used to select components of the synthetic promoters, rather than the method of construction. Specifically, the methods used to select the cis-regulatory elements that make up each new promoter are the focus of the patent estate. Each synthetic regulatory sequence that the company develops is patentable, providing a way for the company to use its IP as a competitive advantage.

Synthetic promoters can be used in research tools, diagnostics or therapeutic applications.

In January 2015, Synpromics entered into an alliance with UniQure to develop synthetic promoters with up-regulated liver cell specific activity and that are suitable for gene expression with an adeno-associated virus (AAV) vector. In June 2016, Synpromics announced that it had successfully produced promoters of less than 250 bp in length that showed high levels of activity, and that the 2015 agreement had been extended to create ultrasmall synthetic promoters.

In January 2016, Synpromics partnered with Cell Therapy Catapult to develop gene-expression promoters to drive a high level of viral vector yield from new stable cell lines. The objective is to develop a better way to produce vectors that have much higher titers and are more efficient. Viral vectors that are the focus of this collaboration include retrovirus and AAV. The end application is in the gene therapy industry.

SYNTHACE LTD.

The London Bioscience Innovation Centre
2 Royal College Street
London NW1 0NH
U.K.
Tel: 44-20-7554-5877
Website: www.synthace.com

Synthace Ltd, founded as a spinout from the University College London, is developing a synthetic-biology platform based on computational modeling and big data analysis. The platform can be used to rapidly engineer and optimize biologic production systems for producing specialty chemicals.

Synthace's main platform, Antha, allows for designing and performing experiments with a user interface, and then analyzes the results.

In April 2016, Synthace formed an alliance with Microsoft to deliver the Antha platform on Microsoft's Azure Cloud service.

In October 2015, Synthace formed a partnership with Dow AgroSciences to develop better microbial production strains for agricultural applications.

SYNTHETIC BIOLOGICS INC.

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Rockville, MD 20850
Tel: 301/417-4364
Fax: 301/417-4367
Website: www.syntheticbiologics.com

Synthetic Biologics Inc. is developing drugs for treating infectious diseases. Lead projects include SYN-004, an oral enzyme for preventing C. difficile infection, and SYN-010, for treating irritable bowel syndrome with constipation.

Synthetic Biologics has a collaboration with Intrexon to develop and commercialize synthetic-biology-derived mAb therapies for treating infectious diseases. Synthetic Biologics uses Intrexon's ActoBiotics platform for delivering proteins and peptides to the gastrointestinal tract through food-grade microbes.

This collaboration addresses the pressing problem of multidrug resistant bacteria, as mAbs may be able to destroy the microbes and neutralize their toxins. Lead candidates under this collaboration include SYN-005 and SYN-200.

SYN-005, in preclinical development, is a combination of two humanized antibodies including hu1B7, for treating critically ill infants with pertussis. SNY-200, still in discovery, addresses patients with PKU, a metabolic disorder.

SYNTHETIC GENOMICS INC.

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Tel: 858/754-2900
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Website: www.syntheticgenomics.com

Synthetic Genomics (SGI) was founded in 2005 by J. Craig Venter. It is a broad-based synthetic-biology company, with strategies in the key market segments of metabolic engineering, synthetic genes and genomes, and drug discovery. SGI is developing a suite of synthetic-biology products that rely on uniquely engineered microorganisms to perform specific metabolic functions.

The company's competitive advantages include access to state-of-the-art DNA-sequencing technologies, DNA-synthesis technology and genomics expertise through the Craig Venter Institute for Genomic Research. These capabilities allow SGI to explore the genomes of selected species at high resolution, followed by re-engineering its genomes to improve specific functions.

SGI has achieved a number of synthetic-biology milestones during the past several years. In July 2010, the company created the first synthetic cell. In May 2013, the first synthetic influenza vaccine was developed using synthetic hemaggutinin and neuraminidase genes, which were transfected into canine kidney cells for vaccine manufacture. In March 2016, the company constructed the first viable minimal cell, JCVI-Syn3.0, which contains 473 genes and 531 kilo bp.

SGI is focusing on bioproduction, including proprietary synthetic host systems. The company markets to the life sciences research industry, and uses its core technologies together with business partners to develop applied products in health (flu vaccines, gene/cell therapy, biologics, organ transplants and antimicrobials), nutrition (dietary supplements, food ingredients, omega 3 oils and algal protein) and bio-industrial (renewable chemicals, bio-based intermediates, plant enhancement and protection, and algal biofuels).

SGI markets a range of synthetic biology reagents to laboratories and production facilities, including three products involving Gibson Assembly: HiFI 1-Step, Ultra, and Site-Directed utagenesis Gibson Assembly Kits.

In September 2015, SGI extended an earlier collaboration with Lung Biotechnology to develop transplantation-ready pig organs using SGI platforms. In particular, the partners will use SGI's DNA design, synthesis, genome-editing and genome-modification tools to engineer primary pig cells' genomes. Lung Biotechnology will use its xenotransplantation know-how to implant these engineered cells to create pig embryos that develop and are born with human-transplantable organs. The initial target market will be transplantable kidneys for treating end-stage renal failure.

SGI is working on a microorganism that can be used as a workhorse host organism for the biotechnology industry and that would function like E. coli but with a much faster growth rate. The microorganism, called Vmax, is a modified version of Vibrio natriegens, a marine bacterium. The goal is to commercialize Vmax cells for molecular cloning and protein expression.

In July 2016, SGI formed an alliance with VWR, a leading global provider of products and services to laboratories and production plants. This agreement enhances SGI's marketing of synthetic biology reagents, including the Gibson Assembly DNA cloning suite of products.

In June 2015, SGI licensed a wide range of DNA-synthesis technologies that it had acquired from Febit to the gene-synthesis company Gen9 Inc. The agreement provided Gen9 with valuable microarray-based high-throughput DNA synthesis to complement its core synthesis technology based on Agilent chips and the BioFab platform with unique error correction methodology. The agreement thus provided Gen9 with a way to tailor its synthesis procedures based on a client's specific needs to optimize volume, cost and efficiency.

SYNTHORX INC.

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Tel: 858/750-4700
Website: www.synthorx.com

Synthorx Inc., founded in 2014, is developing synthetic DNA bases for synthetic-biology applications, including discovery of novel medicines, diagnostics and vaccines. Synthorx exclusively licensed rights to synthetic-biology technology involving synthetic DNA bases from the Scripps Research Institute (San Diego, Calif.).

In 2014, the company's cofounder, Dr. Floyd Romesberg, reported on the first example of a semisynthetic organism capable of maintaining and replicating a synthetic base pair in its DNA[6].

[6] Romesberg et al., A semi-synthetic organism with an expanded genetic alphabet, *Nature*. 2014, 509, 385–8.

The platform allows the incorporation of nonnatural amino acids into proteins, thus improving their performance. The potential is for better designed biotherapeutics to address previously undruggable targets.

SYNVITROBIO INC.

953 Indiana Street
San Francisco, CA 94107
Tel: 646/725-6686
Website: www.synvitrobio.com

Synvitrobio Inc., founded in 2015 as a spinout from the California Institute of Technology, provides synthetic biology engineering services.

Synvitrobio is developing a cell-free synthetic-biology platform that allows for rapid prototyping of design-build-test cycles. The company is addressing an industry need to streamline the present cell-based workflow for developing and testing microbial factory systems.

Cell-free systems mimic the in vivo environment and can generate relevant biologic data but do not have the restrictions of cellular systems, thus reducing the cost and time for development.

TAXA BIO-ENGINEERING

Suite 230, 665 3rd Street
San Francisco, CA 94107
Tel: 415/779-6333
Website: www.taxa.com

Taxa Bio-Engineering, founded in 2013 as Glowing Plant, is using synthetic biology to create bioluminescent systems in plants. The company empowers the nonscientific community to perform synthetic biology by offering protein engineering, DNA assembly, transient experiments and stable transformation services.

Customers have access to a library of standardized parts, including promoters, terminators and selectable markers.

Plant species that are available for transformation include *Arabidopsis* and *Nicotiana tabacum*, with others in development (rose, petunia, poinsettia) or planned (tomato, lettuce, canola, squash/zucchini and lily).

TEEWINOT LIFE SCIENCES CORP.

12005 Whitmarsh Lane
Tampa, FL 33626
Tel: 813/501-5021
Website: www.tlscorp.com

Teewinot Life Sciences Corp. is developing cannabinoid-based therapeutics using a synthetic-biology platform.

Cannabinoids are produced using synthetic biology, biocatalysis, chemical synthesis, bioinformatics and metabolomics platforms. By producing synthetic cannabinoids, Teewinot hopes to be less expensive than the current method of growing cannabis plants and extracting the cannabinoids. Also, synthetic methods allow production of cannabinoid prodrugs and cannabinoid analogs at high purity that cannot be manufactured using the cannabis plant.

Teewinot has demonstrated its production technology in multigram per liter scale cannabinoid production in a bioreactor.

TERRAVIA HOLDINGS INC.

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South San Francisco, CA 94080
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Website: www.terravia.com

TerraVia Holdings Inc., founded in 2003 under the name Solazyme, is using genetic engineering and synthetic biology to modify heterotrophic algae to produce a range of fatty acid-containing oils. End markets include biofuels, cosmetics and nutrition.

The U.S. FDA has permitted TerraVia to use oils made from one of its algal strains in food products. The main source of revenues is from oil used in skin-care products against wrinkles. TerraVia has a contract with Unilever to supply algal oil to be used in Unilever's Lux branded cosmetics and personal-care products.

In addition to agal oil, TerraVia sells some whole algae products for use in lubricants for oil drilling and in food products (algal proteins and algal flour).

The company has a small pilot plant facility in the U.S. and a larger plant in Brazil. The Brazil plant was developed jointly with Bunge, a multinational agribusiness company that produces the cane sugar feed for the plant.

TESELAGEN BIOTECHNOLOGY INC.

1736-A 18th Street
San Francisco, CA 94107
Tel: 650/387-5932
Website: www.teselagen.com

TeselaGen Biotechnology Inc., founded in 2001, is developing and marketing a rapid bioCAD/CAM prototyping system, called Synthetic Evolution, for synthetic-biology customers. The platform produces DNA sequence assembly instructions that are ready to use on the bench or through automation.

The platform produces scarless DNA, which eliminates uncontrolled scar sequence that can harm DNA efficacy. The platform uses a graphical interface that allows users to design a DNA construct or combinatorial library by arranging individual part icons that correspond to underlying DNA sequences.

The platform is particularly useful for constructing combinatorial libraries, which contain up to several hundred thousand related DNA assemblies, each consisting of different combinations of genes or parts performing similar functions in different organisms. Combinatorial libraries are useful in synthetic biology because they can be screened to find the particular gene combination that has the most productive enzyme pathway in a target host organism.

In April 2016, TeselaGen formed an alliance with Dow AgroSciences to develop a biologic design automation platform for discovery applications in agriculture. The objective is to build a cloud-based platform that can generate cost-optimized DNA construction protocols. This alliance confirms the technical attractiveness of TeselaGen's platform.

THERMO FISHER SCIENTIFIC INC.

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Website: www.thermofisher.com

Thermo Fisher Scientific Inc. (TMO) is the result of a merger in 2006 of Thermo Electron Corp. and Fisher Scientific. TMO provides life science and laboratory analytical instruments, equipment, reagents, consumables and software for research, analysis, discovery and diagnosis. The company operates on a global basis with annual revenues of nearly $17 billion in 2015.

The major business divisions of TMO include Life Sciences Solutions (5% of annual revenues), Analytical Instruments (24%), Specialty Diagnostics (24%) and Laboratory Products and Services (47%).

With major end markets in drug discovery, research, biopharma services, molecular diagnostics and genomics, TMO has a large stake in synthetic-biology tools, as evidenced by its acquisition of Life Technologies Inc., completed in February 2014.

In synthetic biology, TMO distinguishes itself by offering an extensive range of tools and by its geographic coverage. TMO's strategy is to offer a complete line of synthetic-biology tools to the research markets. The objective is to provide a synthetic-biology workbench to customers.

Synthetic-biology businesses include DNA sequencing, gene synthesis, cell culture media and bioinformatics.

Tools that Life Technologies offers include CRISPR/Cas9 (genome editing), GeneArt Precision TALs (genome editing), GeneArt Strings (custom DNA fragments), custom gene

synthesis, GeneArt Seamless cloning and genetic assembly kits, algae engineering kits, Vector NTI sequence analysis and design software, Ultimate ORF clones (premade clones), GeneArt Site-directed mutagenesis Plus Kit and GeneArt directed-evolution services.

TOUCHLIGHT GENETICS LTD

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Touchlight Genetics Ltd. is commercializing a novel in vitro DNA amplification platform for producing next-generation DNA products.

The Touchlight amplification process produces closed linear DNA constructs, called doggybones (dbDNA). Advantages of this platform include high yield and scalability, amplification of complex secondary structures and repetitive sequences, no antibiotic resistance genes or bacterial sequences and a low error rate.

TRANSCRIPTIC INC.

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Transcriptic Inc., founded in 2012, runs biology experiments for scientists using robotics and the cloud. The company’s services allow synthetic-biology researchers to access a fully automated cell and molecular-biology laboratory from a web browser. Experimental design, automation and analysis are included.

Synthetic-biology protocols can be automated and streamlined using the Transcriptic services. For example, Transcriptic workcells can automate enzyme-designed site-directed mutagenesis, which is traditionally slow to do and is susceptible to errors.

A key feature of Transcriptic’s platform is liquid-handling robots. These robots introduce efficiency, reliability and repeatability into the synthetic-biology workflow. For customers, there are no start-up costs.

TRITON ALGAE INNOVATIONS LTD.

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Triton Algae Innovations Ltd. uses synthetic biology to develop and market algae that produce high-value proteins.

Triton's subsidiary company, Wellsea Nutrition, markets a digestive-health supplement, Comfortin, that uses engineered green algae, *Chlamydomonas*, with natural healing properties. Comfortin helps to soothe intestinal discomfort and support normal digestive health.

The company's main platform, PhycoLogix, modifies algae to produce complex proteins, enzymes and other biologics in a range of industries. The main proteins marketed include Osteopontin, MAA (mammary associated amyloid) and LHN (lactadherin). Osteopontin helps to support bone growth/resorption and increases wound healing. MAA helps to stimulate production of a mucus coating in the digestive tract. LHN supports the immune system and helps to maintain the health of the intestinal mucosa.

TWIST BIOSCIENCE

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Twist Bioscience, founded in 2013, is developing and commercializing a next-generation platform for DNA synthesis. The company is using microarray-based methods to synthesize DNA. Oligonucleotides are synthesized within holes inside of the nanowells on Twist's wafer. Oligonucleotides can be combined together to build a gene by depositing one oligonucleotide into each of the nanowell holes.

Enzymes for combining the oligonucleotides are also added to the nanowells. The advantage of this approach is that small volumes of oligonucleotides are used and the process can be easily scaled up to producing thousands of genes. Each silicon wafer can contain up to 10,000 nanowells.

In April 2016, Twist acquired Genome Compiler Corp. (Israel), which strengthened its position in the synthetic DNA industry.

In April 2016, Twist completed a deal with Microsoft in which Microsoft purchased 10 million bp of DNA for evaluating its use in computer data storage. DNA can be potentially used as storage because of its long lifespan (thousands of years) and high storage density (one trillion gigabytes per gram of DNA).

In June 2016, Twist formed a partnership with Desktop Genetics to supply experimental designs and DNA-synthesis tools for gene-editing research applications. Desktop Genetics will provide its single-guide RNA CRISPR library design services and Twist will provide its guide libraries for editing of gene targets.

This collaboration complements the earlier acquisition of Genome Compiler by providing customers an integrated workflow for CRISPR design and oligonucleotide pools.

VERDEZYNE INC.

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Verdezyne (formerly called Coda Genomics), founded in 2005 as a spinout from the University of California, Irvine, is developing synthetic-biology technologies for evolving novel metabolic pathways to produce biofuels and chemicals.

Verdezyne uses a proprietary yeast fermentation technology for producing intermediates used in nylons and other plastics. The company uses a flexible feedstock approach, with the yeast using several plant-based oils and their by-products.

The core of Verdezyne's technology platform is a set of proprietary technologies for the design and assembly of synthetic genes that have high expression and protein production levels. The synthetic genes can be designed to perform well in a range of heterologous hosts and cell-free expression systems. The technology platform includes a bioinformatics package called Translation Engineering that contains a number of tools including HotRod genes, SpeedPlot, Planned Pause Gene Sites and Computationally Optimized DNA Assembly (CODA). The tools are used to design and assemble synthetic genes with optimized expression and function in a range of biologic hosts or cell-free protein-synthesis systems.

The key chemicals that Verdezyne is focusing on include dodecanedioic acid (DDDA), sebacic acid and ADA.

Verdezyne's Biolon DDDA product can be used in nylon 6,12, molding resins, lubricants, adhesives and powder coatings. DDDA is currently produced from butadiene through a multistep chemical process. The addressable market size for DDDA is more than $250 million per year, growing at 5.4% annually.

Verdezyne has an alliance with Cornell Brothers Corp., a large marketer of specialty chemicals in the Asia-Pacific region. The partnership covers sales and distribution of Biolon DDDA in this region. Verdezyne produces Biolon DDDA in a plant in Malaysia.

Sebacic acid is used in the production of nylon 6,10, coatings, adhesives and polyester resins. Sebacic acid is now produced using castor oil, which is in limited supply and which creates the deadly poison ricin. The market size for sebacic acid is $400 million per year, growing at a 5.5% annual rate.

ADA is used in nylon 6,6 and thermoplastic polyurethanes. ADA is now produced using benzene, which is a carcinogenic petroleum fraction. The global market for ADA is $6.3 billion per year, growing at a 4.6% annual rate.

ZIOPHARM ONCOLOGY INC.

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ZioPharm Oncology Inc. is a clinical-stage company developing immune-oncology therapies through collaboration with Intrexon Corp. Through an agreement with Intrexon, the company holds specific rights to Intrexon's synthetic immuno-oncology technology for oncology applications.

ZioPharm's clinical stage product candidate is Ad-RTS-IL-12, which is being evaluated in combination with the oral activator veledimex for treating metastatic melanoma and unresectable recurrent or metastatic breast cancers. When a patient takes the pill containing the activator, the IL-12 (antitumor cytokine interleukin 12) gene is expressed. Conversely, when the patient stops taking the pill, the IL-12 expression stops. This permits dosing at set times, thus providing an important safety benefit.

The RheoSwitch (Intrexon's proprietary biologic switch) controls the IL-12 gene expression. ZioPharm has an R&D pipeline of multigenic therapies that are controlled by the Intrexon RheoSwitch Therapeutic System.

ZioPharm, through its agreements with the University of Texas MD Anderson Cancer Center and with Intrexon, holds licenses to a range of technologies, including the following: CAR-T-cell therapies; nonviral gene transfer systems; genetic modification and/or propagation of immune cells and other cellular therapy approaches; natural killer cells; and TCRs.

ZYMERGEN

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Zymergen, founded in 2013, is developing microbial systems for industrial biology by using advanced tools in synthetic biology, automation, machine learning and data architecture.

Zymergen uses a range of microbes, including gram-positive and gram-negative bacteria and various fungi.

In March 2016, Zymergen formed an alliance with Arzeda in which new microbial strains will be developed and manufactured. The alliance will use Arzeda's pathway and enzyme

design tools (Archytas protein-design software, Scylax pathway design software) and Zymergen’s strain-engineering technologies.

