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SYNTHETIC BIOLOGY

Long-term Opportunities in the Bioeconomy

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A REVOLUTION IN SCIENCE

Of the long-term trends that will shape the future of our world, few hold the transformative promise of synthetic biology. Its potential is such that comparisons with the industrial revolution do not risk hyperbole. It enabled the rapid development of the Covid-19 vaccine and explains the meat-free burger in your favourite fast-food outlet. And yet we appear only to be at the beginning of this journey. Few corners of today's economy will remain untouched by its evolution.

But what exactly is synthetic biology? A quick search of the internet throws up myriad definitions. Confusingly, there are also multiple appellations in use that mean broadly the same thing – molecular biology, computational biology, bioengineering, biotechnology, among others.

For the purposes of this paper, we use synthetic biology as an umbrella term for a range of technologies and techniques that aim to manipulate biology for a variety of ends. The primary goal of synthetic biology is to gain access to cells to write new and better biological code, and it owes its development to a confluence of disciplines across biology, chemistry, technology, engineering, and computer science. As such, it stands in the vanguard of multidisciplinary science.

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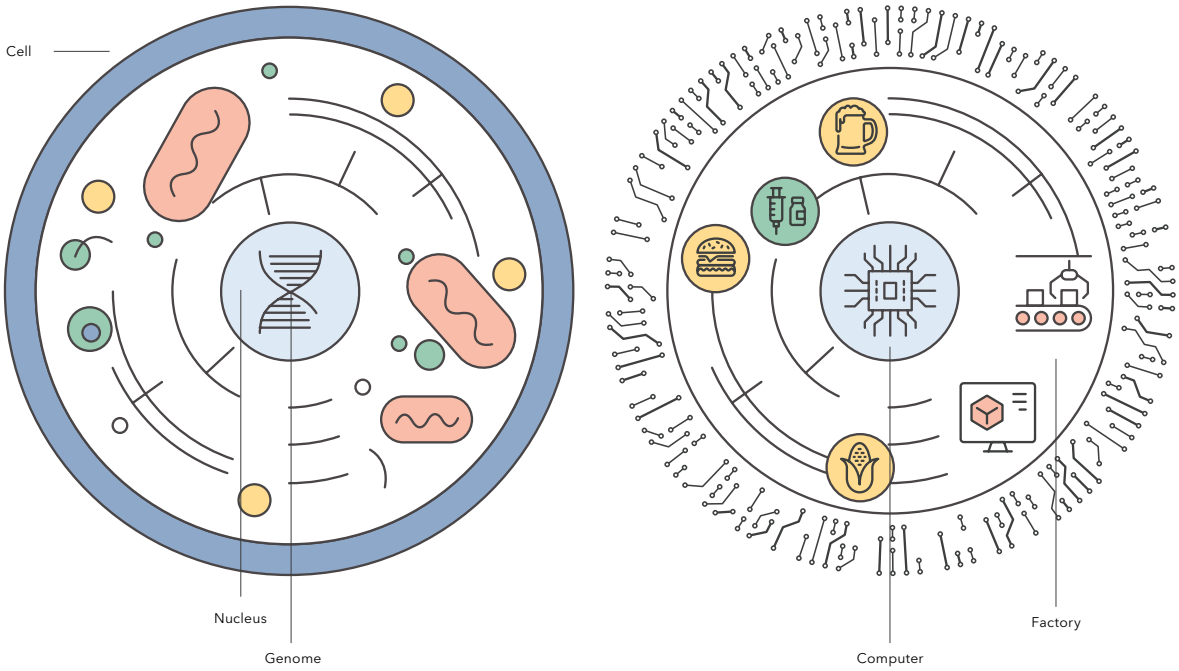
Synthetic biology looks to the future whilst drawing heavily on the past. It has been shaped by some practices and technologies that have been around for hundreds of years, whilst others have only emerged very recently. It may still be in its infancy, but it has already produced world-changing outcomes in healthcare and a variety of industrial applications.

THE COMPUTER AND THE FACTORY



The most obvious benefits of synthetic biology to date have been in how we tackle, treat, and prevent chronic and serious diseases. Pivotal developments include the synthesis of insulin to treat diabetes; designing antibodies to target cancer cells; developing mRNA vaccines in response to the Covid-19 pandemic; and the newer frontiers of gene therapies. Previously untreatable diseases have come into scope.

In fields other than healthcare, synthetic biology is at a much earlier stage of development. Lab-grown meat, for example, or the alteration and improvement of the nutritional value of food. Some uses are well established, however. Enzymes in washing detergent have been with us for many, many years, whilst the use of yeast in brewing dates back millennia. Over time, synthetic biology will have a profound impact on much that we manufacture and consume.

Fundamentally, we stand on the cusp of an acceleration in the evolution of synthetic biology because of the convergence of our ability to read, write and edit genetic code with exponential strides in computer power, big data and artificial learning. As this coming together drives down costs and more technologies become commercially viable, synthetic biology's impact will only grow.

For investors, this will create opportunities as well as risks across multiple sectors and industries. Some incumbents will be disrupted, whilst others will thrive. New winners and sources of profit will emerge. Understanding synthetic biology is essential for any long-term investor.

THE COMPUTER AND THE FACTORY

Synthetic biology has been facilitated by discoveries that allow us to programme genes and control cells. In their book "The Genesis Machine" Amy Webb and Andrew Hessel encourage the reader to think of the gene as a computer and the cell as a factory.

Like a computer, the gene is based on digital code and can store vast amounts of information. The gene controls the function of the cell. The cell is like a "high-tech, fully automated" factory that can produce an almost infinite variety of outputs, mostly proteins. It has its own power station, cells within cells called mitochondria, that can be fired up by different energy sources. Cells make up every living thing and produce everything that is created in biology – from the human brain to a spider's silk.

From Aristotle's Lyceum and Darwin's Beagle to Cambridge University and Silicon Valley, our understanding of genes and cells – the computer and the factory – is the accumulation of centuries of philosophical and scientific enquiry.

A HISTORY OF SYNTHETIC BIOLOGY

The convergence of three broad and interwoven categories of technology – the reading, writing, and editing of DNA – accelerated by advances in computing and artificial intelligence, explain the significant breakthroughs of recent years in synthetic biology. Yet synthetic biology is not a static discipline; it is constantly evolving, building on centuries of prior scientific progress. As the Nobel Prize-winning biologist Sydney Brenner noted:

"Progress in science depends on new techniques, new discoveries and new ideas, probably in that order."

Of course, Brenner's statement is circular, whereby new ideas yield further new techniques, and therefore finding a start to synthetic biology is challenging. In fact, the mystery of heredity, namely how biological information is passed down the generations, has captivated the brightest minds for millennia. In *Generation of Animals*, Aristotle logically deduced that heredity involved the inter-generational transmission of information. It is for this key insight that scientists have joked that the venerable philosopher should be awarded the Nobel Prize for the discovery of DNA. Another 2000 years would pass before our understanding of DNA was propelled forward in the wake of the Enlightenment, and the epoch-defining theories of Charles Darwin.

Darwin's theory of natural selection and evolution is well understood. The question that plagued the rest of his life was to then explain how hereditary information was passed down through the generations – how genetic mutations transpired and subsequently remained constant throughout species. To match Darwin's theory of evolution, Gregor Mendel's theory of heredity solved this challenge. Born into a German-speaking family in what is today the Czech Republic, Mendel was a seemingly unremarkable Augustinian monk who had twice failed the natural

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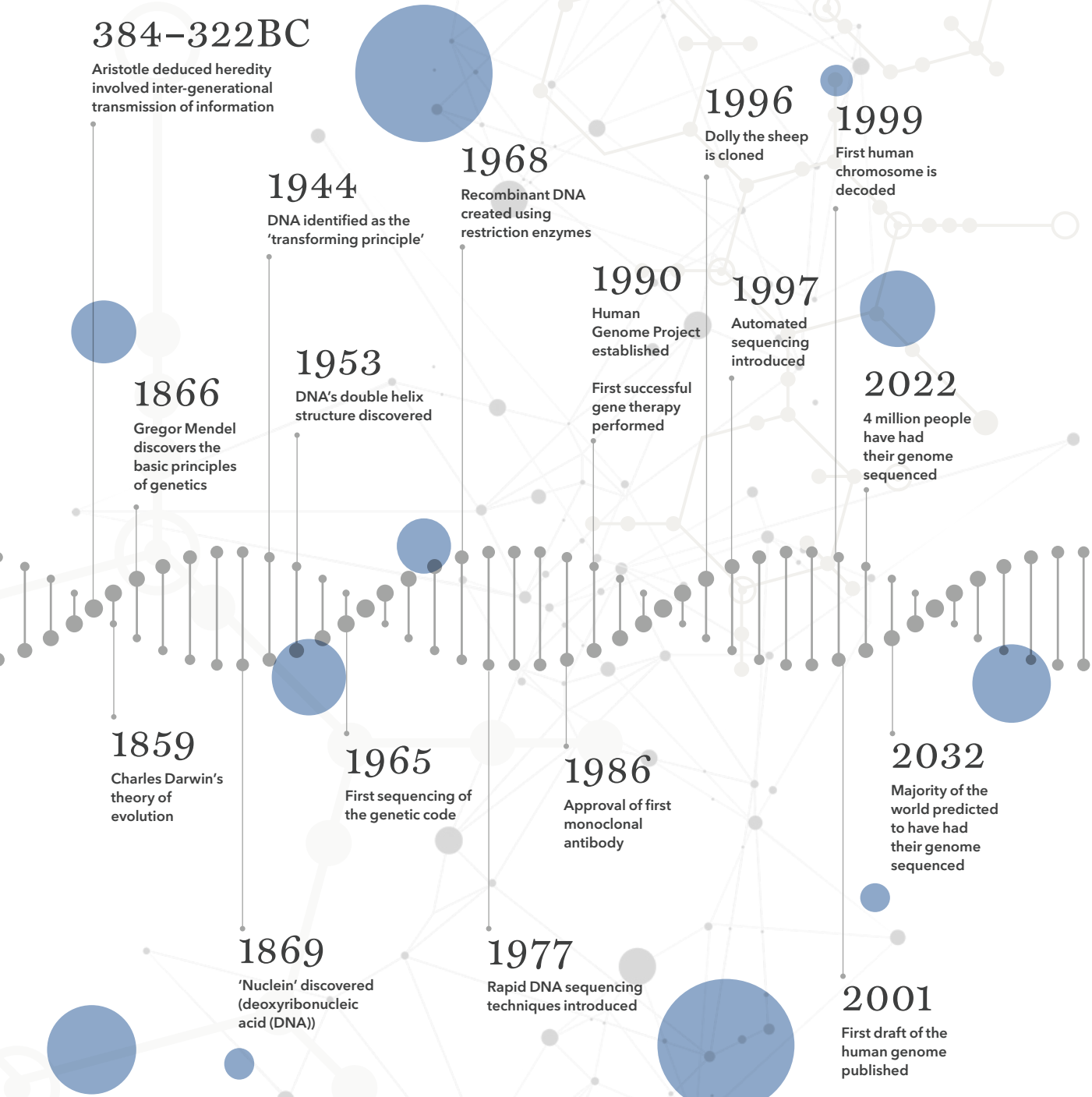
DNA TIMELINE



DNA double helix structure

sciences exams that would have allowed him to pursue a career as a high school teacher. Nevertheless, it was through more mundane matters – planting pea crops throughout the 1850s - that he etched his name in scientific history. By meticulously recording the physical characteristics of offspring from cross-bred pea plants over more than eight years, Mendel mathematically deduced the presence of indivisible and discrete units of heredity.

By the turn of the 20th century, the broad theory of heredity, coined genetics by William Bateson in 1905, was thus in place. As such, the first part of the century concerned itself with turning the abstraction of indivisible units of heredity (genes) into an understanding of their physical form and method of function. The journey involved sea urchins, the breeding of tens of thousands of fruit flies, and none other than Erwin Schrödinger of 'Schrödinger's cat' fame. These experiments culminated in another milestone in the history of synthetic biology's roots. In 1953, the minds of Watson, Crick, Franklin and Wilkins combined (unwittingly) to solve the three-dimensional structure of DNA (the double helix). At long last, humanity understood the physical structure of the material substance that was fundamental to biology's processes.

The latter half of the 20th century focused on building on this understanding by further zooming in on the structure of DNA, with the most fundamental breakthrough of DNA sequencing commonly attributed to Frederick Sanger, of the eponymous Sanger Method. Coinciding with and accelerating developments in DNA sequencing, were advances in the manipulation and synthesis of the molecule. DNA editing traces its roots back to the 1960s and the creation of recombinant DNA using restriction enzymes, which serve to "cut and paste" DNA.

This approach grew in sophistication until the discovery of CRISPR-Cas9 in 2012, which can very precisely disrupt, delete or correct a genome. DNA synthesis began a little earlier, with the first chemical synthesis of DNA in 1955. Much like DNA sequencing and editing, this technology has improved exponentially over the years. By printing genes onto a silicon chip, Twist Bioscience's approach has increased the scale and throughput of DNA synthesis by over 10,000x.

With constant advances in all three, mutually inclusive, technologies, synthetic biology began to yield tangible applications along the way.

With constant advances in all three, mutually inclusive, technologies, synthetic biology began to yield tangible applications along the way. Notable examples include the creation of synthetic insulin, the approval of the first monoclonal antibody in 1986, and the first successful gene therapy performed in 1990. Our ability to read, edit and synthesise DNA reached such a level by the turn of this century that the first draft of the human genome was published in 2001.

The above transition from understanding the gene's structure and how it functions, to its manipulation and synthesis, is the story of synthetic biology. It is due to these developments that we are now equipped with tools that provide us with sufficient understanding of the inner functioning of our cells and the ability to engineer them to produce a litany of proteins. These tools will continue to improve at an ever-accelerating rate, allowing the scientific community to compound its understanding of synthetic biology and invent new products based on the technology. Indeed, we have just experienced the largest possible proof point of synthetic biology's capabilities – the mRNA vaccines, to which we will turn our attention later.

ELI LILLY, NOVO NORDISK AND THE STORY OF INSULIN

The history of human insulin is foundational to the story of synthetic biology. It is also a clear demonstration of the technology's ability to harness the cell's machinery to produce vital proteins which would otherwise be difficult to source from nature. Further, it suggests that harnessing the cell's tools can lead to extremely lucrative profits. Indeed, in 2022, **Eli Lilly**, **Novo Nordisk** and Sanofi together generated more than US$20bn in revenues from the sale of insulin for the treatment of diabetes.

The discovery of insulin as a therapeutic occurred in the early 20th century with the extraction, grinding and reinjection of pancreases from, and back into, dogs. This distinctly unglamorous work by the Canadian scientists Frederick Banting and Charles Best now serves as the foundation of one of the most important drugs in modern medicine. As the reinjection of insulin yielded normalised levels of blood sugar in the subject dogs, the pair turned to cattle from which they could source far greater quantities of pancreases from local meatpacking houses. In 1922, the first human patient was successfully treated with the product. As a result of this discovery, Banting and Best were awarded the Nobel Prize for Medicine in 1923.

The University of Toronto, where Banting and Best were housed, licensed the technology to pharmaceutical companies such as Eli Lilly, Novo Terapeutisk and Nordisk Insulinlaboratorium (the latter two merging to form Novo Nordisk in 1989). Lilly had been founded by the eponymous Colonel Eli Lilly in 1876, who tasked his employees with "Take what you find here and make it better and better." That spirit clearly endured down the generations, with Lilly's grandson, Eli Lilly Jr., playing an instrumental role in insulin's progression from animal-derived to synthetically produced. Nordisk Insulinlaboratorium's origins also date back more than a century, when two travelling Danish scientists obtained permission to manufacture and sell Banting and Best's discovery back home in Denmark. Novo Terapeutisk was founded shortly after by two brothers who had initially worked for Nordisk.

As the 20th century progressed, the population of diabetics increased at a faster rate than pharmaceutical companies' ability to source pancreases from cattle and pigs. By 1978, over 56 million animals per year were needed to meet Eli Lilly's demand alone. The product was also imperfect – its beneficial effects wore off quickly and allergic reactions were frequent. The sub-par product and increasing challenge of the supply constraints led Eli Lilly Jr. to begin the search for alternatives. Whilst the initial focus was on developing insulin from different animals, a small group of scientists discovered an ingenious alternative.

Operating out of an aircraft hangar in South San Francisco, Genentech performed numerous experiments on bacteria, engineering the microbes to produce insulin, eventually finding success in 1978. The process involved recombinant DNA technology, whereby the scientists would synthesise two sequences of DNA, transplant each into two separate bacterial strains, and then recombine the output (amino acid chains) to form a complete insulin molecule. This principle of harnessing the uniquely elegant machinery of a cell to produce a complicated molecule underpins all synthetic biology. Genentech received a twenty-year contract from Lilly to develop and scale Humulin (the first commercially available biosynthetic human insulin) and the firm enjoyed three decades of success as a standalone entity. In 2009, Swiss pharmaceutical giant **Roche** bought the world's oldest biotechnology company for $47bn, having owned a majority stake in Genentech since 1990. The combination is the basis of Roche's expertise in cancer immunotherapy today.

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THE STORY OF NEXT-GENERATION SEQUENCING

The fundamental technology on which next-generation sequencing (NGS) is based was initially developed in the chemistry department at the University of Cambridge in the late 1990s. It was at this very same university that Watson and Crick put the finishing touches to their double helix model half a century earlier. The decades in between yielded an exponential improvement in our ability to sequence DNA, both in terms of cost and precision.

Following the discovery of the double helix model, attention turned to understanding how a series of nucleotides, linked together as adenine-thymine and cytosine-guanine base pairs, was able to create proteins. To do this, we first needed to be able to determine the order of these chemicals to find the hidden code within.

Initial attempts were time-consuming, often inaccurate, and only capable of sequencing chains of 10-25 base pairs (oligonucleotides). For context, the entire human genome is over three billion base pairs in length. The major leap forward in DNA sequencing that occurred in the 1970s was in part due to developments in the complementary technologies of DNA synthesis and editing. As a result, two ground-breaking technologies emerged in 1977, with one proving to be the foundation for the next few decades of DNA sequencing (the scientist behind the other method had to be content with a Nobel Prize). Frederick Sanger discovered an ingenious method that involved the radiolabelling (a process for tracking the movement of molecules) of DNA fragments, also known as the "chain termination method". With this method, Sanger sequenced the first complete genome in history, that of a type of virus that infects E.coli.

Despite Sanger's discovery, DNA sequencing remained a manual process, something that needed to change if scientists were to sequence three billion base pairs. Improvements on Sanger's method came in the form of fluorescent dyes, which removed the need for radioactive reagents. With the elimination of radioactive material, significant advances in the automation of workflows were possible. Applied Biosystems' automated sequencer, the ABI Prism 3700, made it possible to sequence thousands of bases daily. The ABI Prism 3700 also played an instrumental role in a forthcoming project that would seek to fully sequence the entire human genome. The Human Genome Project (HGP), launched in 1990, sought to achieve its goal within 15 years. By 2003, the HGP had managed to sequence over 90% of the entire human genome, costing an approximate $3 billion.

Not only was the ABI Prism 3700 a game-changer due to its automation of the Sanger process, but also because of its generation of data for analysis onto a computer, removing the need for manual data entry. Constant improvements based on this data allowed scientists to sequence one million bases (one megabase) in a day by the mid-1990s.

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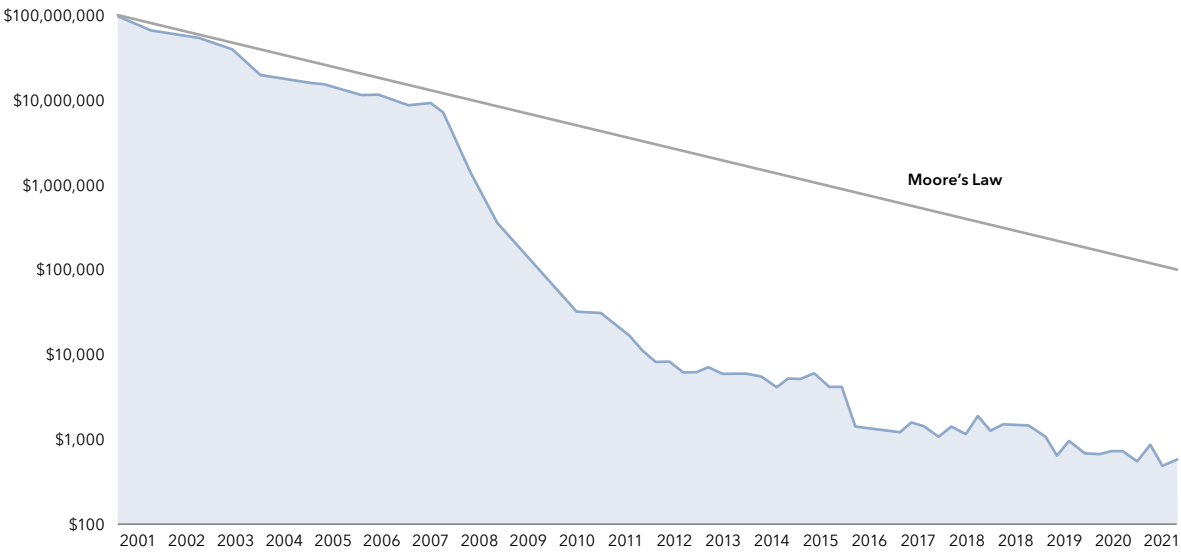
Building on this, a second generation of DNA sequencing emerged, known as next-generation sequencing technology or high-throughput sequencing. Pioneers of this approach again resided at the University of Cambridge, forming the company Solexa in 1998. Seven years later, Solexa's instrument sequenced the entire genome of the very same virus sequenced by Sanger thirty years prior. Following the commercial launch of its Genome Analyzer in 2006, San Diego-based **Illumina** acquired the business for $600m. Today, Solexa's technology serves as the basis for a company with 80% share of the global NGS sequencing market. New entrants are attempting to create a market for an even newer generation of sequencing technologies.

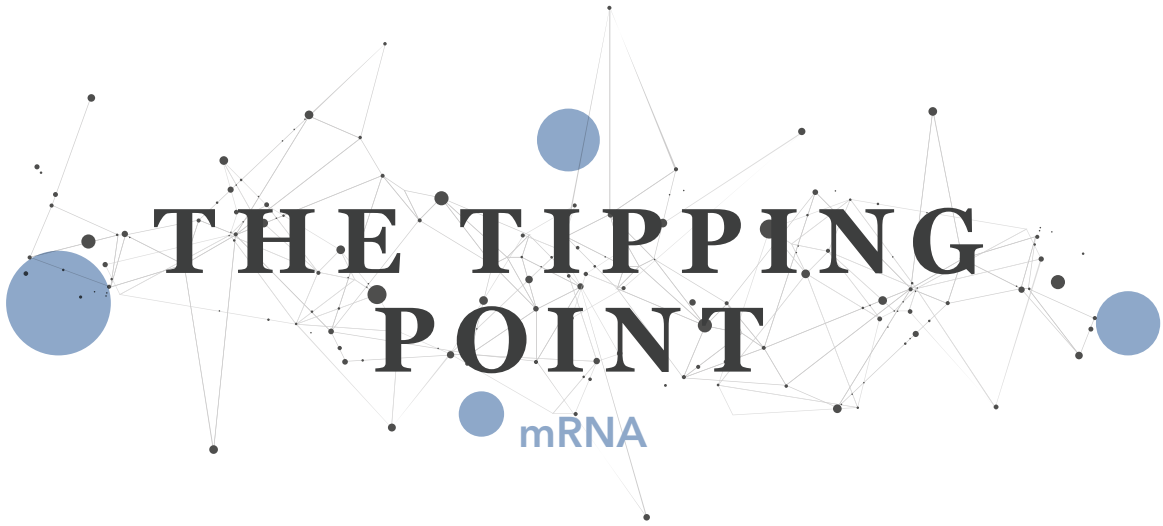
The graph below shows that the rate at which the cost to sequence a human genome has decreased over the past twenty years, exceeds that of Moore's Law. While the HGP took 15 years and cost $3 billion, **Illumina's** latest iteration of its sequencing instruments, the NovaSeq X Series, targets $200 per genome, whilst the more expensive NovaSeq X Plus Series can sequence over 20,000 genomes per year.

Today, just 4 million people have had their genome sequenced. **Illumina** ambitiously expects most of the world's population to have done so multiple times over the coming decade. The potential that such a democratisation of technology holds is profound, whether it be for disease screening, companion diagnostics (tailoring a specific therapy to a patient's genetic profile), or pre-natal testing.

COST PER HUMAN GENOME



Source: National Human Genome Research Institute



Within the space of two weeks in November 2020, Pfizer/BioNTech and Moderna announced Phase 3 trial results related to the efficacy of their respective vaccines against Covid-19. Not only did the vaccines demonstrate efficacy of well above 90% (and close to 100% against severe Covid-19), but no less encouraging was the speed with which these drugs were developed, going from design to clinical trialling to emergency-use authorisation in less than one year.

As such, these vaccines heralded the advent of a new class of therapies: mRNA medicines. Put simply, the roll-out of the Covid-19 vaccines in 2020 sparked a significant breakthrough in the adoption of mRNA technology from a commercial, regulatory and societal perspective. Its successful application signals the potential for the technology to be used to treat a range of previously untreatable diseases and genetic defects, as well as offering alternatives to existing treatments that may not be highly efficacious and/or have debilitating side effects.

The promise of mRNA technology is that a human's cell, upon receiving instructions from mRNA, can make an exact replica of a sophisticated protein, either to target evasive antigens or to replace faulty or missing proteins. This process already occurs naturally, whereby information stored in DNA is copied to mRNA which then is "read" by the cell's ribosomes to "print" proteins. Each cell produces hundreds of millions of proteins every day in this manner. The aim is to therefore write a set of instructions in the form of modified mRNA manufactured externally to take advantage of this process.

The idea of using mRNA to instruct human cells to make a protein *in vivo* is the result of decades of experimentation and false starts and can be largely attributed to the painstaking work of two scientists, Katalin Kariko and Drew Weissman. Hungarian-born Kariko had long held the belief that mRNA could be used to instruct the human

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body to produce proteins with therapeutic potential. In the face of opposition from the scientific community due to the unorthodoxy of her ideas, she persisted in her experimentation, moving from laboratory to laboratory despite near-constant concerns regarding funding. Eventually, she partnered with Drew Weissman at the University of Pennsylvania, with whom she discovered a way to modify mRNA (more specifically uridine, one of four key nucleotides) to avoid undesired immune responses. It is this technology that serves as a key foundational pillar of mRNA medicines today.

After building up evidence of mRNA's therapeutic potential, Kariko and Weissman caught the attention of the two pioneering firms in the field - Moderna and BioNTech. Founded in 2010, Moderna existed primarily as a research-stage company until IPO in December 2018. Up until that point, the company had given little away about its novel technology. BioNTech was established in 2008 by husband-and-wife team Uğur Şahin and Özlem Türeci.

Both BioNTech and Moderna had developed extensive pipelines prior to Covid-19, but it was the pandemic that presented the ultimate opportunity for the validation of the technology. With this validation achieved, both now have billions of dollars of cash on their balance sheets to fund the next generation of mRNA therapies. They have been joined by an ever-expanding number of other players, such as France's Sanofi, which has acquired Translate Bio and Tidal Therapeutics; Germany-based CureVac, and the UK's AstraZeneca, which has partnered with VaxEquity. That list will expand over the coming decades as more companies invest in the potential of mRNA.

There are additional benefits to mRNA technology beyond those of disease cure and prevention. Unlike gene editing, mRNA does not stay in the cell permanently and has no impact on the body's DNA. Because the manufacturing process is cell-free, mRNA medicines do not need to be 'scaled up' in bioreactors, which significantly reduces the quantity of raw materials used relative to other types of drugs. Companies can also automate and rapidly scale this process from clinical to commercial production and share infrastructure across drug candidates (it was this ability to scale quickly that enabled hundreds of millions of Covid-19 vaccines to be shipped in 2021 and 2022). Furthermore, even simple changes to the code of mRNA allow for new medicines to be developed in a matter of days or weeks before beginning human trials.

NEXT STEPS

Whilst estimates vary, hundreds of thousands of deaths every year are attributed to seasonal flu. Alongside coronaviruses, influenza viruses are contagious respiratory diseases. It is for this reason that companies are looking to leverage technology to enter the flu market, both in terms of producing a separate therapeutic to Covid-19 vaccines, but also to create a combination vaccine that targets flu, Covid and other respiratory viruses, helping to reduce healthcare costs and increase compliance from a population resistant to the idea of multiple jabs.

The flu vaccination industry totals tens of billions of dollars and involves extremely well-capitalised pharmaceutical companies, such as Sanofi, GSK and **CSL**. Yet there is a significant opportunity to improve the standard of care through the unique benefits of mRNA. Currently, those developing annual flu jabs rely on predicting the upcoming winter's flu strains in the early part of the year given the time it takes to grow the active ingredient in bioreactors. This time lag leads to efficacy rates that rarely exceed 60% due to further mutations of the virus by the time the flu season arrives.

By contrast, mRNA medicines can compress the development timeline and therefore allow for the sequencing of strains that are in circulation significantly closer to the flu season. Moderna has already achieved something similar with its boosters against Covid-19 variants. The ambition is therefore to create a vaccine that has much higher efficacy rates. Recent trial results have been mixed, but work on improving efficacy continues.

LONGER-TERM POTENTIAL

The opportunities in mRNA are ever-growing and proposed therapies continue to proliferate. Current pipelines include therapeutics targeting latent viruses, such as HIV, and rare metabolic diseases. Others aim to restore the growth of blood vessels in the heart and improve the treatment of cystic fibrosis.

> As we strive to lead healthier and longer lives, mRNA promises to be a significant and complementary addition to our already formidable medical arsenal.

Cancer is also very much in scope, with the potential to leverage mRNA technology to create so-called 'personalised cancer vaccines' (PCV). In truth, 'vaccine' is something of a misnomer, given these treatments do not work like a vaccine in the traditional preventative sense. Instead, they seek to treat the cancer or slow its progression.

PCVs are precisely engineered treatments that are suited to an individual's specific tumour mutations. Following a biopsy that helps to identify the most prevalent mutations of a patient's cancer, a PCV can be developed that produces patient-specific neoantigens (tumour-related antigens) in the immune system. This stimulates the immune system to attack the neoantigens via T cells. The ambition is to enhance recent breakthroughs in immunotherapy by boosting a patient's quantity of T cells.

Most recently, Moderna and Merck announced that their approach to combine the latter's Keytruda oncology drug with the mRNA vaccine significantly reduces the risk of dying from melanoma, a form of skin cancer, compared to a patient receiving Keytruda alone. Moderna and Merck expect the trial to move to Phase 3 in 2023, and to further expand their research to additional tumour types.

We are clearly in the very early stages in the development of mRNA medicine, and it will likely be years before more therapies pass Phase 3 trials and are commercialised. Whether or not companies can generate substantial and recurring revenues from Covid-19 booster jabs misses the longer-term implications of this technology's ability to treat pervasive, complicated and previously incurable or under-treated diseases. It may also increase the success rate of new drug development and therefore reduce healthcare costs. As we strive to lead healthier and longer lives, mRNA promises to be a significant and complementary addition to our already formidable medical arsenal.

LIPID NANOPARTICLES – THE UNSUNG HEROES

An mRNA therapeutic is dependent on three broadly-defined components – the chemistry and engineering of the mRNA, the delivery technology, and the manufacturing of the entire therapeutic itself.

In terms of the delivery technology, in most instances, mRNA particles are wrapped in protective lipid nanoparticles (LNPs). LNPs are fatty globules that shield the mRNA from the body's defence mechanisms (enzymes found in the blood and interstitial fluids) and deliver it into cells, where the mRNA is used to make proteins.

LNPs comprise four components – ionisable lipids whose positive charges bind to the negatively charged backbone of mRNA; pegylated lipids that help stabilise the particle; and phospholipids and cholesterol molecules that contribute to the particle's structure. LNPs are the most clinically advanced delivery system for mRNA particles, and they took more than three decades to perfect.

When injected intravenously, the particles accumulate in the liver, raising the prospect of being able to use LNPs to treat forms of liver cancer. Research is also focusing on a delivery mechanism that can reach other organs, boosting the potential for using mRNA vaccines for other tissue and cell-based diseases.

WHAT EXACTLY IS mRNA?

The US National Cancer Institute offers the following definition of mRNA *"A type of RNA (ribonucleic acid) found in cells. Messenger RNA (mRNA) molecules carry the genetic information needed to make proteins. They carry the information from the DNA in the nucleus of the cell to the cytoplasm where the proteins are made."*

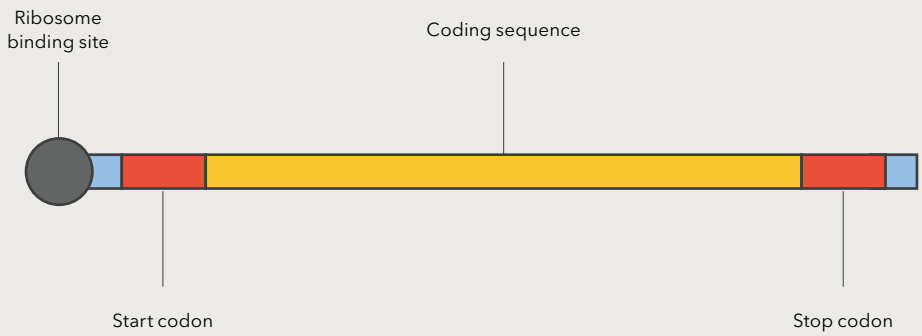
mRNA acts as an intermediary between the genetic information contained in DNA and the amino acid sequence of proteins. It is a linear polymer containing four monomers called nucleotides, the sequence of which form a language made of three-letter words called codons. These codons signal where protein synthesis should begin, what protein to make, and where synthesis should end. This process is referred to as translation as the mRNA is reading in one language and outputting in another. Every cell has hundreds of thousands of mRNA producing millions of proteins every day.

Storage
DNA stores instructions for proteins in the nucleus

Software
mRNA is a temporary set of instructions for cells to make a protein, mRNA is made using DNA

Applications
Proteins form the basis of life by performing the functions required by every cell, proteins are made using mRNA

TYPICAL STRUCTURE OF AN mRNA MOLECULE



SYNTHETIC BIOLOGY IN ACTION

HEALTHCARE

By far the most widespread application of synthetic biology has been in healthcare. The development of biologic drugs has revolutionised the treatment of myriad diseases and previously untreatable conditions. Unlike traditional, chemically synthesized small-molecule drugs, biologics are produced from living organisms or contain components of living organisms, such as proteins, tissue, DNA, or cells. Biologic 'modalities' include vaccines, blood products, monoclonal antibodies, gene and cellular therapies, and peptides.

For a long time, the world was primarily reliant on small-molecule drugs. Pharmaceutical companies have historically been chemical specialists, producing powerful, frequently ground-breaking drugs through chemical synthesis. By targeting the body in a general manner, however, these small-molecule drugs often produce damaging side effects. Chemotherapy, for example, kills bad cells, but destroys good ones as well.

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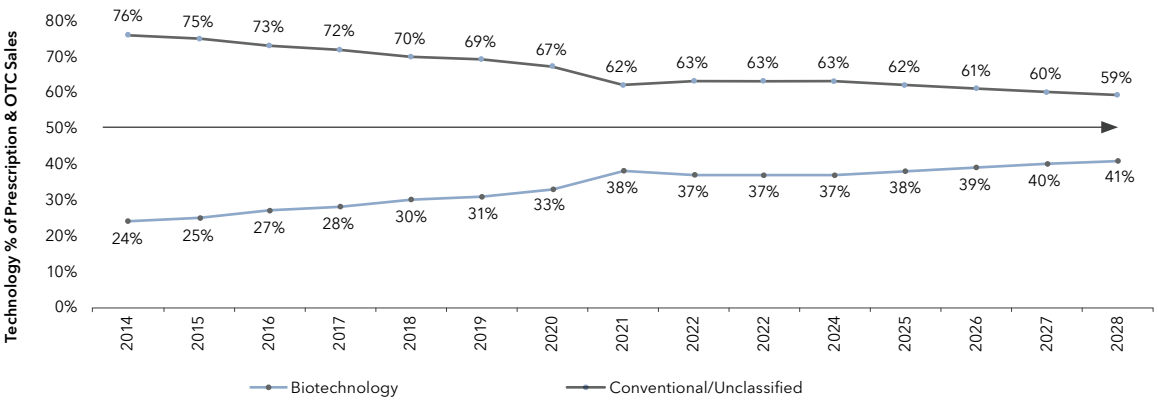
Biologic drugs work in a more targeted way. This greater precision has facilitated a vast array of new therapies, particularly in the treatment of cancers. They are also typically less toxic, generating fewer side effects. Larger and more complex than their small-molecule counterparts, a biologic drug consists of tens of thousands more atoms than a small-molecule drug. Today, this is a $370 billion market and the growth area of the pharmaceutical industry.

BIOLOGICS ENTER THE MAINSTREAM

Biologics share of the pharmaceutical market has risen steadily over many years (chart 1), receiving a significant boost during the Covid-19 pandemic with the development of mRNA vaccines. Over the last 20 years, there has been a gradual shift in investment from small-molecule drugs to biologics, to the point where the former now outnumber the latter in the top 100 pharmaceutical products. It is likely biologics will soon constitute a majority share of the wider drug market.

CHART 1: A LONG-TERM TREND TOWARDS BIOLOGICS

Worldwide prescription drug and OTC pharmaceutical sales: biotech vs conventional



Source: Evaluate World Preview Report, October 2022.

An important caveat to note, however, is the disparity between revenues and volumes. According to IQVIA, in 2017 biologics accounted for 37% of US net spending on prescription drugs, but only 2% of the drugs prescribed by physicians. More expensive to develop, manufacture and administer, biologics cost significantly more than small-molecule drugs. This raises challenging questions for the industry, regulators and policymakers around affordability and access, a topic we will return to later.

Despite, or perhaps even because of these cost issues, the march of biologics shows few signs of abating. Whilst new drug approvals in the US were down by around 25% in 2022, biologic approvals exceeded those of small-molecule drugs for the first time, a landmark in the development of the technology.[1] Biologics have become the primary growth engines of the world's large pharmaceutical companies, with R&D spend and investment pivoting accordingly. Not only will this pipeline drive the overall growth of the market, but it will bring incipient modalities into the mainstream, marking another stage in the biologics revolution.

THE ADVENT OF MONOCLONAL ANTIBODIES

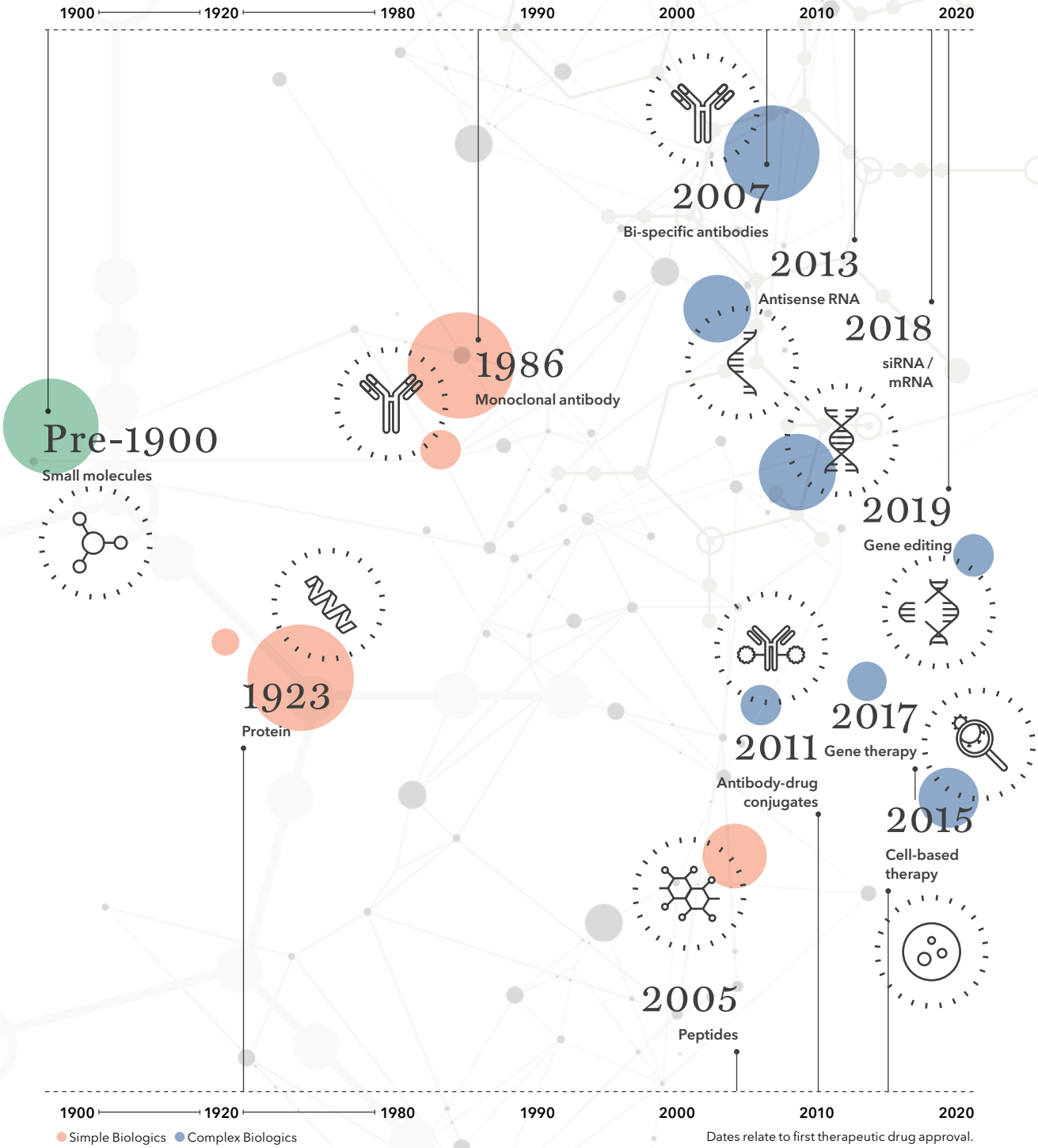
Genentech's use of recombinant DNA technology to clone and then produce human insulin on an industrial scale heralded the first generation of biologic drugs. The next evolutionary step was the development of monoclonal antibodies (mAB).

Genentech's use of recombinant DNA technology to clone and then produce human insulin on an industrial scale heralded the first generation of biologic drugs.

Monoclonal antibodies are laboratory produced proteins that act like substitute antibodies in the body. They enlist the body's immune system to fight disease and have transformed the diagnosis and treatment of numerous diseases, most notably cancer. The word "monoclonal" refers to the fact that the antibodies created are clones of one specific antibody.

[1]www.nature.com January 2023

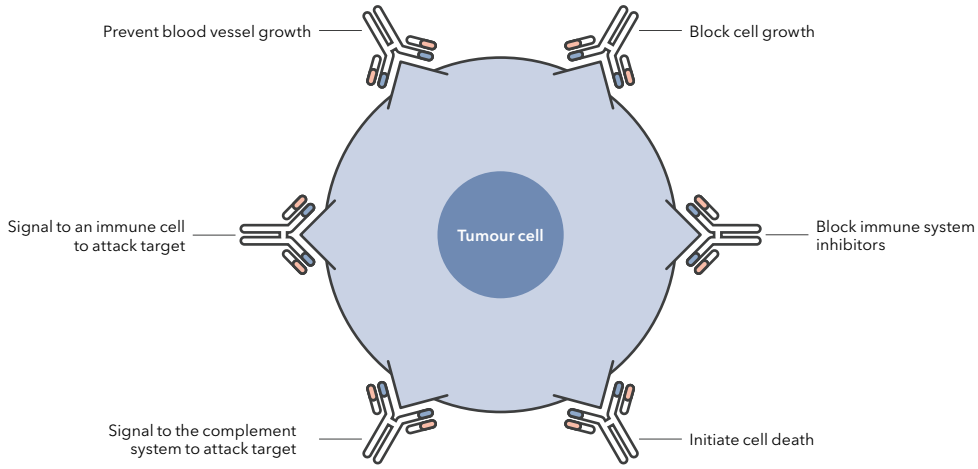
MULTIPLYING MODALITIES



Monoclonal antibodies are produced using a process called cell culture and hybridoma technology. Immune cells are taken from a living source, typically a mouse, that has been injected with a specific antigen. These cells are then combined with cancer cells to create a hybrid cell line that produces a selected antibody. This hybrid cell line is then used to produce large quantities of the required monoclonal antibody. Today, monoclonal antibodies are the most important drugs in the portfolios of many of the world's major pharmaceutical companies, including **Novartis** and **Roche**.

By binding to receptors on a target, such as antigens on the surface of cancer cells, monoclonal antibodies can perform a wide range of functions, some of which are shown in the image below.

Monoclonal antibodies revolutionised biological research, providing the foundations for the use of antibodies as therapeutics as well as for diagnostic applications. And whilst they remain the dominant modality, new generations of antibody drugs are emerging, marking a shift from standard monoclonal antibodies to highly complex formats.

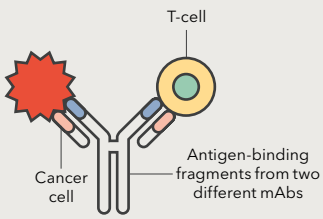


MULTIPLYING MODALITIES

Recent years have seen an explosion of innovative biological modalities, ranging from antibody-drug conjugates and mRNA-based drugs to cell and gene therapies. These new modalities accounted for around one-third of all approvals in the US in 2022.

Bispecific Antibodies

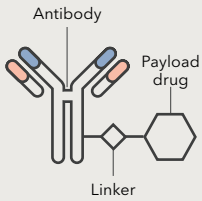
Bispecific antibodies (bsAbs) combine two or more antigen-recognising elements in one molecule to bind to two or more targets using a chemical linker. They are used in tumour immunotherapy, as well as in the treatment of diseases such as haemophilia A, diabetes, and Alzheimer's. The clinical therapeutic effects of bsAbs are superior to those of monoclonal antibodies.



Whilst monoclonal antibody drugs target a single antigen, diseases can be complex and have multiple drivers. In certain diseases, for example, cells may respond to the inhibition of one receptor by producing more of a second receptor to circumvent

the impact of the drug. BsAbs aim to treat complex diseases by engaging two targets with one molecule. This dual targeting leads to improved target selectivity and has the potential to enhance efficacy alongside reduced systemic toxicity.

Antibody-Drug Conjugates



Like a highly targeted, biologic equivalent of chemotherapy but without the debilitating side effects, antibody-drug conjugates (ADC) harness the targeting abilities of monoclonal antibodies by linking them to cell-killing agents. ADCs are considered extremely potent anti-cancer treatments.

An ADC links cytotoxic cancer drug molecules to antibodies. The antibody portion of the ADC can be designed to target specific proteins found primarily on a tumour cell, with the aim of delivering the cytotoxic payload more directly and reducing the collateral damage to healthy tissue.

In practice, the antibody component of the ADC binds to an antigen on the surface of a cancer cell before being internalised inside the cell. The ADC is subsequently broken down and the cytotoxic payload released, initiating cell destruction.

Cell & Gene Therapy

Cell therapy and gene therapy are evolving rapidly, promising material long-term benefits to people suffering from myriad diseases, from ophthalmological disorders to cancer. Cell and gene therapies can be combined or used individually.

By injecting new, healthy cells into a patient, cell therapy replaces or repairs diseased or damaged cells. These healthy cells can come from either the patient, known as autologous cell therapy, or a donor, known as allogeneic cell therapy.

Gene therapy seeks to alleviate or cure genetic diseases by inactivating defective genes, correcting faulty genes and replacing them with healthy genes, or adding new, healthy genes. Effectively, gene therapy aims to treat disease at the source.

Gene therapy can be delivered in one of two ways: *in vivo* and *ex vivo*.

In vivo gene therapy involves the direct delivery of a modified and therapeutic gene into a patient. Successful applications to date include the treatment of haemophilia, neurological disorders, and a range of eye-related conditions, such as glaucoma.

Ex vivo gene therapy involves the modification of genes outside the body. Target cells are removed from the body, modified and returned to the patient. Ex vivo gene therapy is most frequently used to treat blood-related disorders, such as leukaemia and lymphoma.

BIOPROCESSING

MANUFACTURING BIOLOGICS

If we return to the analogy of the cell as factory, the process of manufacturing biologics, known as bioprocessing or biomanufacturing, centres on the engineering of a cell to produce a desired product.

Bioprocessing consists of two distinct stages: production and purification. The first 'upstream' phase includes the isolation of the cell line to be produced, growing those cells at the required scale, and harvesting. The subsequent 'downstream' stage involves the purification of the bioproduct collected at the end of the upstream stage to create a final product that meets the necessary standards of safety and quality.

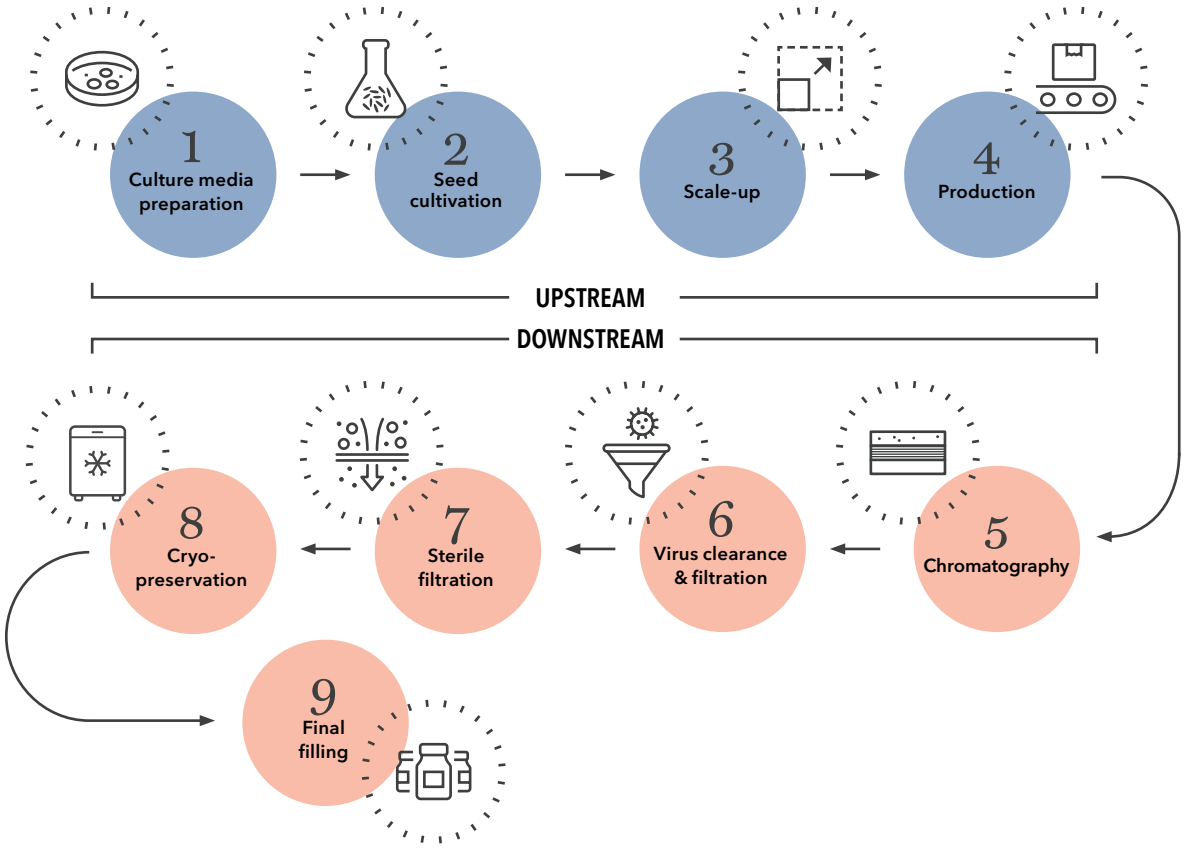
During the process, cells are cultivated in bioreactors that get progressively larger until the final industrial production scale is reached, typically several thousand litres. This is known as 'scaling up'. This bioproduct must then be recovered, concentrated, and purified using multiple techniques, including separation and filtration. Each litre of the scaled-up bioproduct might yield only a few grammes of the final product.

The principles of bioprocessing are simple: to produce the largest possible quantity of the desired product to as high a quality as possible in the shortest amount of time. But because the process deals with inherently variable living organisms, it is characterised by significant complexity and variability. Seemingly minor changes can have a major impact across the process. Every end-product is different to the one that came before it and will function differently in the body.

The process of manufacturing biologics, known as bioprocessing or biomanufacturing, centres on the engineering of a cell to produce a desired product.

Complexity and variability introduce significant risk into the biologics manufacturing process. Increasingly, this is not a risk the pharmaceutical companies wish to assume. For this and other reasons, there is a growing trend towards

BIOPROCESSING IN ACTION



outsourcing the bioprocessing function. Enter the contract development manufacturing organisations, or CDMOs.

SHARING THE BURDEN

Carrying echoes of the semiconductor foundry industry, where players such as **Taiwan Semiconductor** provide outsourced manufacturing services to chip designers, CDMOs offer outsourcing services to global pharmaceutical companies throughout the lifecycle of a drug, from development and small-scale production for clinical trials to commercial-scale manufacturing.

For the pharmaceutical companies, enlisting the support of a trusted CDMO makes a great deal of sense. Not only does it outsource the complexity and capital intensity of bioprocessing to an expert third-party, but it frees the pharmaceutical company to focus more on its core competency of drug discovery. CDMOs also assume the growing regulatory and testing burden. Whereas the manufacturing process for a small molecule drug might be subject to 40-50 quality control tests, a biologic can face more than 250.[1]

For a drug company, selecting a CDMO is a significant strategic decision. Technical competence, operational

> Estimated to be worth US$184 billion in 2021, the CDMO market is predicted to grow to US$290 billion by 2027.

LONZA – IN THE VANGUARD OF THE BIOLOGICS REVOLUTION

In May 2020, during some of the darkest days of the Covid-19 pandemic, the global biotech firm Moderna entered a 10-year strategic collaboration with **Lonza** that would see the latter manufacture the former's novel coronavirus vaccine. In just eight months and while grappling with workplace pandemic restrictions, Lonza had constructed manufacturing facilities and commenced production of Spikevax.

The resilience, innovation and technical expertise that enabled Lonza to meet unprecedented delivery targets would surely have resonated with the company's founding fathers, although the business itself would be entirely unrecognisable from the one they knew. Founded in the late 19th century by a group of German industrialists and Swiss financiers, Lonza originally operated hydroelectric generators where the river Lonza flows through the canton of Valais in the Swiss Alps.

Over the next 100 years, the company would morph from a straightforward electric utility into a diversified and complex industrial conglomerate. And it was in the 1980s and 90s that Lonza took its first tentative steps into a market that would define its future direction. Leveraging its existing chemistry expertise, the company entered the fast-growing biotechnology sector, providing manufacturing and ancillary services for the global pharmaceutical industry. Some four decades on, it is the world's leading CDMO.

No CDMO can match Lonza for geographical reach, breadth of service and technical capability. From its major manufacturing sites in the US, Switzerland, Singapore and China, Lonza serves the manufacturing needs of a global and diverse client base, from small biotech firms with limited in-house production capacity, more than half of whom use Lonza as a single-source supplier, to the large global pharmaceutical giants, who typically outsource a portion of their manufacturing.

As the only CDMO with a presence across all major biologic technologies, Lonza is estimated to have 20% market share in the global biologics CDMO market, a figure that rises further in rapidly growing niche areas, such as antibody-drug conjugates.

The 'stickiness' of this business provides the company with a stable and recurring revenue stream. Underpinned by long-term contracts, more than two-thirds of Lonza's revenues are highly predictable.

Lonza is investing heavily to maintain its industry-leading position. The most high-profile manifestation of this investment is the recently opened Ibex Solutions facility, a campus of five state-of-the-art manufacturing plants nestling in the Swiss Alps not far from where Elektrizitätswerk Lonza built its first hydroelectric generators.

Providing customers with agility and flexibility across the entire product lifecycle, the complex supports multiple biologic technologies and was integral to the rapid development of Moderna's Spikevax. In an industry where speed-to-market matters – the first and second drugs released onto the market will typically dominate sales – Ibex symbolises Lonza's commitment to maintaining its place in the vanguard of the biologics revolution.

flexibility, risk management capabilities, and a proven track record of delivery and compliance are key considerations. Once a trusted relationship is established, they tend to last. Only rarely will a customer switch CDMO.

Estimated to be worth US$184 billion in 2021, the CDMO market is predicted to grow to US$290 billion by 2027.[2] Outsourcing penetration is thought to be in the region of 30-40%. That figure is considerably higher for new biologic modalities; innovation in biologics is driven primarily by small biotech firms that have no interest in building a manufacturing capability. And in a further echo of the semiconductor foundry industry, the CDMO landscape is increasingly consolidating around a handful of scale players: **Lonza**, **WuXi Biologics**, Catalent, and Samsung Biologics.

[1]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3564302/
[2]https://www.mordorintelligence.com/industry-reports/pharmaceutical-contract-development-and-manufacturing-organization-cdmo-market

SYNTHETIC BIOLOGY IN ACTION II

BEYOND HEALTHCARE

Whilst healthcare remains the focus of the bulk of the work in synthetic biology, there is a growing ecosystem of researchers and companies exploring its use in other industries.

The reason for this is clear. Synthetic biology provides the tools to produce two broad outcomes that have applications across a whole gamut of sectors. The first is the potential to replace existing products with better, cheaper alternatives, manufactured at scale by cell factories. The second is the use of the machinery of a cell to create an entirely new product that would not be possible using chemical or industrial methods.

Whilst still very much in its infancy, synthetic biology is already making a difference to commercially available products in food, agriculture and consumer goods. It is safe to assume that any industry which produces or is dependent on the use of a chemical or naturally derived product that is unsustainable and/or expensive could find itself disrupted by synthetic biology.

It is the open-ended nature of this scenario that has led to imprecise, but directionally correct, estimates regarding its potential impact. In a 2020 study, McKinsey suggested that up to 60% of the world economy's physical inputs could be produced biologically.[1] A transformation on this scale will have profound implications for societies and economies, bringing with it risks as well as opportunities for investors.

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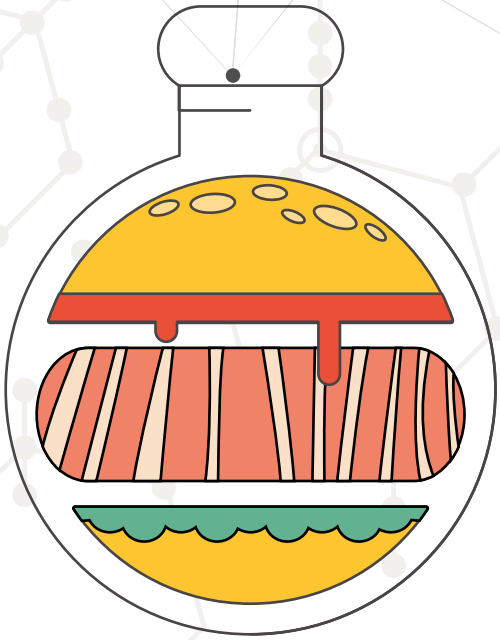
Here we consider two sectors of the global economy where synthetic biology is already having a considerable impact, as well as looking at some nascent technologies that may be years from real-world application, but which promise ground-breaking solutions to some of the world's biggest challenges.

FOOD AND AGRICULTURE

The challenges facing the world in food and agriculture are well-documented. According to the United Nations, the global population will reach 9.7 billion by 2050, which



represents another 1.7 billion more mouths to feed than today. And as living standards and wealth increase, so too will demand for animal-based foods.

At the same time, the global food supply chain is facing a dizzying number of challenges, such as extreme weather events linked to climate change, geopolitical tensions, rising transportation costs and associated emissions, labour shortages, livestock diseases, and a decline in arable land. Animal-based food is not only heavily linked to 14.5% of all greenhouse gas emissions, but climate change itself reduces the amount of farmable land available to produce more.[2] Now, however, researchers are using synthetic biology to harness the power of nature in a bid to solve these problems.

The idea of producing food by means of genetic modification is not a new one. In 1931, Winston Churchill argued in an essay entitled 'Fifty Years Hence' that in five decades time "We shall escape the absurdity of growing a whole chicken in order to eat the breast or wing, by growing these parts separately under a suitable medium."

In truth, this simply builds on what humans have been doing for thousands of years. Food production, whether crop or animal-based, has always involved the use of techniques and tools to intervene in and improve on a natural process. What is selective breeding if not a form of genetic modification? For all today's public scepticism around genetically modified organisms, the concept has a long and broadly uncontentious history.

In 1931, Winston Churchill argued in an essay entitled 'Fifty Years Hence' that in five decades time "We shall escape the absurdity of growing a whole chicken in order to eat the breast or wing, by growing these parts separately under a suitable medium."

[1,2]McKinsey Global Institute – The Bio Revolution May 2020

MOONSHOT 1 – DNA DATA STORAGE

In South San Francisco, Twist Bioscience has established a reputation for manufacturing synthetic DNA and DNA products for clients across a range of industries. When we met with the firm at their California headquarters, we discussed its recent work on DNA data storage.

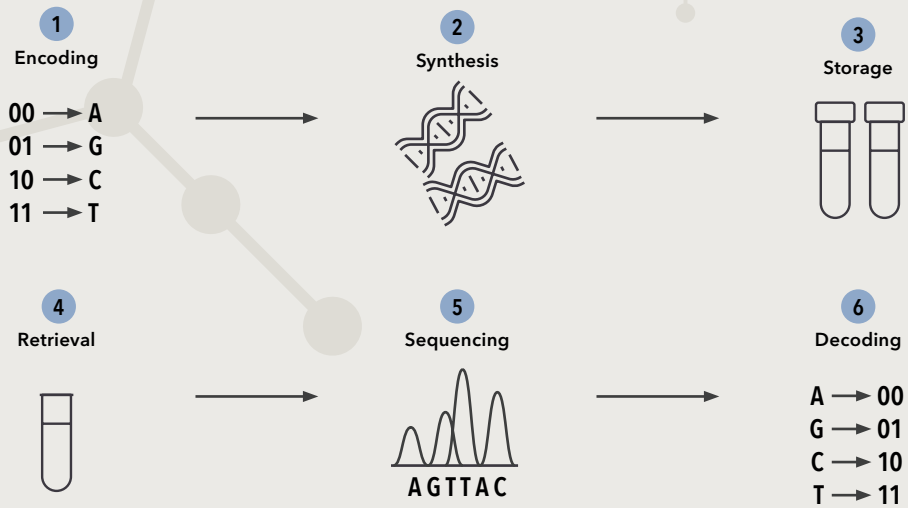
> Whilst current storage technologies have limited longevity and require data migration for long-term storage, DNA is ideally suited to storing vast amounts of data over long periods of time.

In 2020, Twist Bioscience founded the DNA Data Storage Alliance with **Illumina**, Western Digital and **Microsoft** to explore the feasibility of using DNA to store data. The alliance now has thirty-eight members including IBM, Dell and Lenovo.

Whilst current storage technologies have limited longevity and require data migration for long-term storage, DNA is ideally suited to storing vast amounts of data over long periods of time. It is ultra-high density, lasts for thousands of years and can be easily replicated given its inherent properties.

Current storage technologies also require significant amounts of energy, a long-term problem given the exponential growth in data. According to the International Data Corporation, data generated globally is expected to grow at a 23% compound annual growth rate from 2020-2025, reaching 180 zettabytes by 2025 (one zettabyte is equal to one trillion gigabytes).

HOW DNA DATA STORAGE WORKS



It may have taken longer than fifty years, but Churchill's 1931 prediction has become reality. In 2016, Impossible Foods launched the Impossible Burger, a plant-based alternative to the world's favourite fast food. Four years later, the company introduced plant-based alternatives to pork and sausages.

The breakthrough for Impossible Foods was the production of heme, a protein that exists in all plants and animals. Found in haemoglobin, heme is responsible for carrying oxygen in the blood stream. It also gives meat its signature taste. Having identified leghaemoglobin, the heme protein produced by soybeans, as the best substitute for the protein encoded in cows, Impossible Foods then genetically engineered yeast by programming it to make heme molecules.

Whilst still accounting for only a tiny fraction of global 'meat' consumption, the plant-based market has grown rapidly since the arrival of the Impossible Burger. Estimates of its future growth vary, but the environmental benefits of such products are significant. Scientists at the University of Oxford and the University of Amsterdam estimated that plant-based meat alternatives require between 35 and 60 percent less energy, occupy 98 percent less land, and produce 80 to 95 percent fewer greenhouse gases than conventional animals farmed for consumption.

> In 2021, the French luxury goods house Hermès teamed up with biotech firm MycoWorks to manufacture a leather-look version of its Victoria handbag made from sustainable biotextiles.

To date, however, there is little evidence that the increased popularity of plant-based alternatives is having a material impact on the consumption of conventional meat. The challenge appears then to be how to meet that demand in a more sustainable manner. Again, synthetic biology can play a key role. Whilst not yet commercially available, 'cultured' meat is made in laboratories using a process that grows, *in vitro*, muscle tissue that mimics animal muscles and replicates their protein profile.

With consumers increasingly curious about provenance, companies offering alternative, less-impactful solutions have an opportunity to build stronger brands and secure greater customer loyalty.

Sometimes known as 'clean meat' or 'lab-grown meat' cultured meat does not involve the slaughter of animals and has a lower environmental footprint – particularly if renewable energy is used in the production process. More work is required for this to become a commercial reality, not least overcoming public scepticism, but the FDA's approval of Upside Food's lab-grown chicken in November 2022 signalled progress.

Elsewhere, synthetic biology is being used to enhance existing agricultural processes. Rewriting genomes, for example, can help reduce crop losses by altering cellular responses to pathogens or climate change.

More sustainable and targeted alternatives are also replacing harmful and inefficient pesticides. In October 2022, chemical giant Bayer and Ginkgo Bioworks announced a multi-year strategic partnership to focus on areas such as "nitrogen optimization, carbon sequestration, and next generation crop protection". The tie-up builds on an existing joint venture, Joyn Bio, established in 2017 to develop sustainable alternatives to synthetic nitrogen fertilisers.

CONSUMER GOODS

As with food and agriculture, synthetic biology is helping to meet a variety of challenges in the consumer goods space; the manufacture of sustainable plastic-free packaging and the use of synthetic proteins in cosmetics being two high-profile examples.

One of the most successful at-scale commercial applications is Squalane, a plant-derived renewable version of squalene, a naturally occurring skin emollient. In 1910, squalene was discovered in shark liver oil, fuelling years of harvesting that resulted in some shark species becoming endangered and severe damage to marine ecosystems. The need for a more sustainable source was clear. Olives briefly offered hope, but cost, purity, and consistency issues limited uptake.

Enter Amyris, a California-based biotech founded by Jay Keasling, the synthetic biology pioneer behind artemisinin, a malaria treatment derived from extracts of sweet wormwood. Using engineered yeast, sustainable sugarcane, and fermentation technology, Amyris developed Squalane. Today, the company supplies over 50% of the global market, and counts household names like **Estee Lauder**, **L'Oréal** and **Givaudan** as customers.

With consumers increasingly curious about provenance, companies offering alternative, less-impactful solutions have an opportunity to build stronger brands and secure greater customer loyalty.

In fashion too, brands are exploring improvements to production processes that are notoriously carbon and resource intensive. In 2021, the French luxury goods house **Hermès** teamed up with biotech firm MycoWorks to manufacture a leather-look version of its Victoria handbag made from sustainable biotextiles. In this case, the biotextile used was Sylvania, a mushroom-based leather alternative.

Researchers are also using pineapples, grapes and apples to create leather and plastic replacements, with pineapples of special interest given they contain bromelains, a group of proteolytic enzymes that could act as a treatment course for cancer.

MOONSHOT 2 – BIOREMEDIATION

Bioremediation involves the use of microbes to break down polluting substances, whether plastics or other harmful chemicals. It promises to solve the problem of pollution and wastewater contamination through nature.

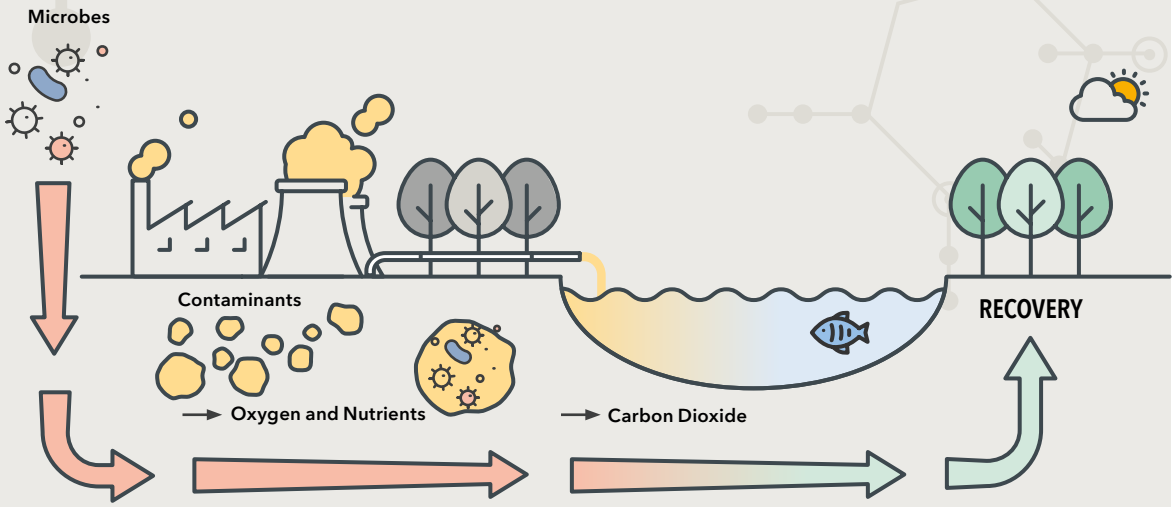
The use of biological processes to treat contaminated wastewater dates to ancient Rome, and more engineered uses are over a century old. In 1989, what came to be known as 'Bioremediation 2.0' came to prominence when fertiliser was used to help clean up the Exxon Valdez oil spill off the coast of Alaska.

Today, Bioremediation 3.0 aims to target the most pernicious and resistant of contaminants – polyfluoroalkyl substances, the so-called 'forever molecules' that are omnipresent in drinking water and linked to cancer.

In 2020, Allonnia was launched with US$40 million in funding from the Ferment Consortium,

The use of biological processes to treat contaminated wastewater dates to ancient Rome, and more engineered uses are over a century old.

Ginkgo Bioworks' investment vehicle that aims to leverage synthetic biology to tackle pressing global challenges. According to Ginkgo's CEO "As one of biology's fundamental roles in nature is to break things down, there is a huge diversity of microbes and enzymes that can clean up waste. This application of biology represents both an enormous market and a worldwide environmental challenge."



UNDERSTANDING THE RISKS

As with all human endeavour, the evolution of synthetic biology has been a continuous process of iteration and learning. The successful roll-out of the Covid-19 vaccines represented not just a breakthrough in mRNA medicines – it also proved to regulators and the wider population that such vaccines could be delivered safely and at scale, allaying fears that some had about medicines that were fast-tracked through the regulatory process. But many risks and concerns remain about synthetic biology. Whilst it has the potential to deliver exciting solutions in myriad areas, its future evolution will not be without hurdles and challenges. Progress is rarely, if ever, linear.

REGULATORY CHALLENGES

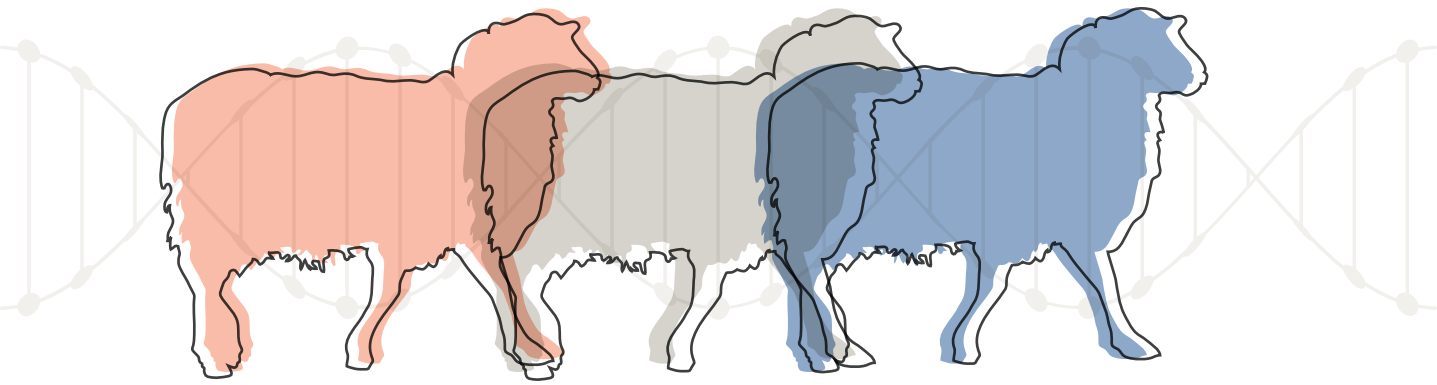
Because of their distinct characteristics and inherent variability, biologics are regulated, tested and controlled differently to small-molecule drugs. To address issues of quality, safety, and efficacy, each batch of a biological therapeutic product must be tested extensively at each stage of production to ensure consistency with prior batches.

Whilst recent years have seen huge strides in our ability to develop biologics safely and consistently, establishing regulatory pathways for the growing array of modalities on the path to commercialisation presents challenges. This is

> Synthetic biology has long raised ethical and moral concerns.

an evolving field, and many regulatory authorities are still building knowledge and experience. To aid this process, the World Health Organisation has established a set of global regulatory standards for new and existing therapies. These aim to ensure consistent manufacturing processes; rigorous clinical studies; and post-approval monitoring of safety and efficacy.

Some new modalities pose distinct challenges to long-established processes. Cell and gene therapies, for example, are often personalised to patients or target conditions with low patient prevalence. As such, finding sufficient patients to conduct traditional clinical trials can be difficult, whilst results based on only small numbers of patients may lack statistical authority. Such barriers are not insurmountable,



but they highlight the challenges facing the industry and regulators as new technologies come onstream. Innovation in the laboratory will need to be complemented by innovation at the regulatory level. Ensuring safety without stifling innovation with excessive regulation is key.

THE MORAL MAZE

Synthetic biology has long raised ethical and moral concerns. The advent of genetically modified organisms generated considerable alarm and headlines about 'Frankenstein' food and led to their banning by some governments. In 1996, Dolly the sheep, the first mammal cloned from an adult cell, was born, sparking ominous warnings of a dystopian future of human cloning and 'designer babies'.

More recently, in 2010, the news that a team of scientists in Maryland had created a human-made cell led to renewed focus on the ethical dilemmas of synthetic biology. At the time, President Obama asked the Presidential Commission for the Study of Bioethical Issues to examine the implications of the emerging science. The resultant paper "New Directions: The Ethics of Synthetic Biology and Emerging Technologies" found that whilst "synthetic biology offers extraordinary promise" it also demands that those in positions of influence have "a duty to attend carefully to potential risks, be responsible stewards, and consider thoughtfully the implications for humans, other species, nature, and the environment."

In 1996, Dolly the sheep, the first mammal cloned from an adult cell, was born, sparking ominous warnings of a dystopian future of human cloning and 'designer babies'.

Whilst there is some evidence that society is becoming more relaxed about some of these ethical concerns (witness, for example, the increased popularity of plant-based meat substitutes) it is likely they will intensify as we progress further along the road of synthetic biology. The ability to edit and write the fundamental building blocks of nature will have profound societal impacts and it will be necessary to balance public trust with scientific progress. Gene therapies that modify a patient's DNA to treat or cure disease will be welcomed by broad swathes of society, whereas genetic enhancements to areas such as IQ will likely encounter greater suspicion.

In truth, we have only begun to scratch the surface of the moral and ethical questions that synthetic biology will pose society. As we progress further down this path, we can

The threats posed to biosecurity are heightened in today's world where geo-political tensions are redrawing regional alliances.

expect to encounter many more dilemmas, few of which will have easy answers.

GETTING TO GRIPS WITH BIOSECURITY

Synthetic biology research is dual-use. In other words, it can be used for good but also for harm – the techniques involved in engineering a bioweapon are the same as those needed to pursue legitimate research. This dual-use functionality poses serious threats to biosecurity.

Biosecurity can be defined as "security against the inadvertent, inappropriate, or intentional malicious or malevolent use of potentially dangerous biological agents or biotechnology, including the development, production, stockpiling, or use of biological weapons, as well as outbreaks of newly emergent and epidemic disease".

Whilst nuclear weapons are expensive to develop, hard to produce and difficult to hide, the basic tools required to synthesise and transmit a deadly virus are increasingly ubiquitous, and the costs to acquire them are falling. It is now relatively easy to access the genetic sequences of highly pathogenic bacteria and viruses, so too the methods for improving their pathogenicity and transmission. Warnings that terrorist groups may be able to construct biological weapons in a domestic setting are not mere scaremongering.

The threats posed to biosecurity are heightened in today's world where geo-political tensions are redrawing regional alliances. In response, countries need to collaborate to create a global system of rules and controls around these technologies, echoing the steps taken to control the use and proliferation of nuclear weapons.

There are numerous practitioner bodies globally that consider biosecurity and related risks. The International Gene Synthesis Consortium, for example, works with governments, NGOs, law enforcement, the synthetic biology community, and other stakeholders to safeguard biosecurity and advance the beneficial applications of gene synthesis technology.

COUNTING THE COST

For all the scientific wonder of the biologics revolution, global patient access to the new therapies has been rather less impressive. Ground-breaking cures and treatments, while greatly welcomed, surely lose some of their lustre if only a privileged few can benefit from their development. Biologic drug use is relatively concentrated in the US market. The rest of the developed world lags the US by some distance and penetration is significantly lower in the emerging economies.

The high cost of biologics and the significant price differential relative to small-molecule drugs are the principal culprits for the present challenges around access. There are several interweaving factors that account for this chasm in cost differential.

- Biologics are far more complex, time consuming and expensive to develop and manufacture.
- Biologics are usually administered by medical professionals at a healthcare facility, unlike small-molecule drugs which can typically be ingested by the patient without oversight.
- There is significantly less competition in the biologics space. The competitive landscape in the small-molecule market is much more mature.

It is also true that we have yet to see the 'biosimilar' market fulfil its promise. Biosimilars are drugs that are 'highly similar' to already approved biologics. Their relationship with the reference biologic can be thought of as analogous to that of small-molecule and 'generic' drugs, although unlike generics, biosimilars are not exact copies. In the same way that cheaper generics typically come onto the market as original drugs came off-patent, thereby lowering costs to patients and healthcare systems, so it was hoped that biosimilars would perform the same function in the biologics market. To date, this hope remains broadly unfulfilled.

The penetration of biosimilars into the US market has been painfully slow, although the situation has been significantly better in Europe. There are several reasons for this lack of progress in the US. Many healthcare payers require the reference biologic, for example, rather than its biosimilar equivalent (a biosimilar must adhere to a more extensive approval process before it can be deemed interchangeable with a brand-name biologic). In Europe, the European Medicines Agency will not approve a biosimilar in the ten years after approving the reference biologic, in the US, that period is 12 years. 'Patent thickets' are also far more common in the US than elsewhere. These complex webs of very often overlapping patents, put in place by the branded

pharmaceutical companies, can be extremely expensive and time consuming to challenge.

Recent bipartisan legislation in the US aimed at supporting biosimilars may help improve accessibility but this is an issue that will likely attract greater scrutiny, both politically and financially, in the years ahead. The longer biologic drugs remain the preserve of those lucky enough to be able to afford them, the louder the calls for regulators and policymakers to act, with potential implications for all stages of the biologics supply chain.

There is a balance to be struck for those grappling with the question of accessibility. To spur innovation, pharmaceutical companies must be granted the requisite patent period to profit from their work. Without this, there would be scant incentive to devote significant time, money, and resource to developing new treatments. But there are also powerful financial and social arguments for encouraging a thriving biosimilar market. According to the Association for Accessible Medicines, biosimilars saved the US healthcare system $7 billion in 2021.[1] With healthcare costs only going in one direction in the years ahead, getting more biosimilars into the market would be hugely beneficial for patients and governments alike.

Despite the existing headwinds, positive progress on adoption and costs is almost certain. As more biologics come off-patent, more players enter the biosimilar market, and as more governments and payers agitate for wider adoption, biosimilars should eventually become as prevalent as generic small-molecule drugs, with the price discount to the reference biologic increasing accordingly. All this may take some time, but it is the most likely resolution to the current cost conundrum.

[1]Association for Accessible Medicines – The US Generic & Biosimilar Medicines Savings Report September 2022

IDENTIFYING THE OPPORTUNITIES

For all the concerns and potential risks outlined in the previous section, synthetic biology promises to deliver enormous societal and economic benefits. It also brings with it significant long-term opportunities for investors.

Further scientific breakthroughs and innovations, when combined with increased computing power, artificial intelligence and automation, mean that synthetic biology will grow rapidly in the years ahead. And as it evolves, it will touch, and in some cases transform, many industries.

Much of the disruption that will be generated by synthetic biology lies many years in the future, particularly in wider industrial applications. Even in healthcare, where its impact is currently greatest, this is a technology still in its relative infancy. But whilst accepting that we have yet to experience synthetic biology's full disruptive force, we believe that the ground-breaking innovation of recent decades has created powerful tailwinds that are supporting durable investment opportunities.

For now, we believe these opportunities are to be found predominantly across the healthcare value chain, from pure pharmaceutical plays to those companies that provide the manufacturing expertise or supply the enabling tools and technology. There is also scope for cautious optimism around nascent opportunities in other sectors.

We believe that the ground-breaking innovation of recent decades has created powerful tailwinds that are supporting durable investment opportunities.

THE VOLUME PLAYERS

As technologies mature and access to the tools underpinning synthetic biology are democratised, volume growth should outpace the growth of the market. For those companies leveraged to volume, this should prove a lucrative scenario – revenues continue to grow nicely, but volumes grow faster. Equipment manufacturers, such as **Sartorius Stedim** and **Merck KGaA**, would be beneficiaries, as would the dominant player in next-generation sequencing,

> Like the semiconductor foundry industry, the CDMO market has been consolidating around scale players, a trend that is likely to continue in the face of increasing technological demands and capital intensity.

Illumina, and **West Pharmaceutical**, the global leader in primary containment consumables for injectable drugs.

THE OUTSOURCED MANUFACTURERS

There is a clear trend towards outsourced manufacturing in biologics. Harnessing the expertise and economies of scale offered by the CDMOs, the established drug developers can avoid taking big bets on building capacity in uncertain drug pipelines and lower their costs. For smaller biotech firms, pairing with a CDMO removes the need entirely to develop an in-house manufacturing capability. Rising geopolitical risks can also be tempered by geographically diversified manufacturing footprints.

Like the semiconductor foundry industry, the CDMO market has been consolidating around scale players, a trend that is likely to continue in the face of increasing technological demands and capital intensity. **WuXi Biologics** and **Lonza** should both be at the forefront of this shift.

THE PHARMA INNOVATORS

The pharmaceutical industry is not an inherently attractive industry for investors. The process of developing new products is not only hugely expensive, but also fraught with the risk of failure. Patent cliffs create revenue challenges, whilst points of genuine differentiation between the big pharma players are often rare. Once-novel technologies eventually become commoditised, available to all for future innovation. The same will happen with synthetic biology.

These challenges demand that investors adopt a highly selective approach. The long-term winners in this space are likely to have durable competitive advantages, such as a clear leadership position in a specific technology – as was the case with Genentech in monoclonal antibodies – or a deeply entrenched position in a large and growing therapeutic area – **Novo Nordisk** in diabetes or **Roche** in oncology.

THE INDUSTRIALS

In time, the impact of synthetic biology will be experienced as profoundly in myriad other industries as it is in healthcare today. For now, however, a degree of caution is warranted, particularly for those investing with a long-term horizon. How and when these nascent technologies translate into sustainable earnings growth, consistent cashflow and enduring competitive advantages is today unknown.

In more established use cases, certain companies do appear well-placed to harness the transformative potential of synthetic biology in their niches. The soon-to-merge (subject to regulatory approval) Danish bioscience companies **Christian Hansen** and **Novozymes** are world leaders in industrial fermentation, a process that underpins the manufacture of enzymes and proteins. This expertise has powered both companies to apply synthetic biology in the production of enzymes and bacterial cultures for a wide range of products, covering human, animal and plant health.

A PARADIGM SHIFT

I think the biggest innovations of the 21st century will be at the intersection of biology and technology. A new era is beginning — Steve Jobs[1]

Whilst we are always alert to the illusory appeal of 'in vogue' subjects, there are some trends that have profound long-term potential. Synthetic biology is one such trend. It has already changed dramatically the healthcare landscape, and in the years ahead it will transform further swathes of the global economy. Whilst many of the changes still to occur can today only be guessed at, there is little doubt that they will drive significant disruption and obsolescence. If investors are to identify the emergent winners and losers from these powerful forces, it will be critical to understand as fully as possible the technologies responsible and their likely application.

The knowledge accumulated by the Walter Scott Research team on synthetic biology in recent years is just the beginning of what will be an ongoing process of rigorous research and analysis. That work, alongside our long-term investment horizon, will stand us in good stead as we continue to seek out for our clients the world-leading companies that will benefit most from this compelling secular growth opportunity.

[1]https://www.azquotes.com/author/7449-Steve_Jobs

GLOSSARY

Amino Acid – Fundamental molecule that serves as the building block for proteins.

Antibody – Protein used by the immune system to identify and neutralise foreign objects like bacteria and viruses.

Antigen – A toxin or other foreign substance which induces an immune response in the body.

Base Pair – Consists of two complementary DNA nucleotide bases that pair together to form a "rung of the DNA ladder".

Cells – The smallest unit that can live on its own. Cells make up all living organisms and the tissues of the body.

Cell Culture – The growth of micro-organisms such as human, plant, or animal cells in the laboratory. Cell cultures can be used to diagnose infections and test new drugs.

Codon – DNA or RNA sequence of three nucleotides (a trinucleotide) that forms a unit of genomic information encoding a particular amino acid or signalling the termination of protein synthesis.

CRISPR (clustered regularly interspaced short palindromic repeats) – A technology to selectively modify the DNA of living organisms.

Cytotoxicity – The quality of being toxic to cells. A cytotoxic agent kills cells, including cancer cells.

DNA (deoxyribonucleic acid) – The molecule that carries genetic information for the development and functioning of an organism.

Double Helix – A term used to describe the physical structure of DNA. A DNA molecule is made up of two linked strands that wind around each other to resemble a twisted ladder in a helix-like shape.

Enzyme – A biological catalyst that accelerates chemical reactions.

Ex Vivo – Outside of the living body. Refers to a medical procedure in which an organ, cells, or tissue are taken from a living body for a treatment or procedure, and then returned to the living body.

Gene – The basic unit of inheritance. Genes contain the information needed to specify physical and biological traits. Genes are made up of sequences of DNA and are incorporated into the genome. It is estimated that the human genome contains 20 to 25 thousand genes.

Genome – Located in the nucleus, the genome is the entire set of DNA instructions found in a cell.

Hybridoma Technology – Common method of producing monoclonal antibodies through the fusion of a short-lived antibody-producing cell and an immortal myeloma cell.

In Vivo – Occurring on or within a living organism.

In Vitro – Occurring in the lab, exterior to the living organism.

mRNA (messenger RNA) – Single-stranded RNA involved in protein synthesis. The role of mRNA is to carry protein information from the DNA in a cell's nucleus to the cell's cytoplasm (watery interior), where the protein-making machinery reads the mRNA sequence.

Nucleotide – The basic building block of nucleic acids (RNA and DNA).

Protein – A large, complex molecule that plays many important roles in the body. Critical to most of the work done by cells and are required for the structure, function and regulation of the body's tissues and organs.

RNA (ribonucleic acid) – Nucleic acid present in all living cells, with structural similarities to DNA.

Ribosome – An intercellular structure made of RNA and protein. The site of protein synthesis in the cell, ribosomes read the messenger RNA (mRNA) sequence and translate that genetic code into a specified string of amino acids.

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