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Synthetic Biology in the Driving Seat of the Bioeconomy

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Synthetic biology is revolutionising the biotech industry and is increasingly applied in previously unthought-of markets. Here, we discuss the importance of this industry to the bioeconomy and two of its key factors: the synthetic biology approach to research and development (R&D), and the unique nature of the carefully designed, stakeholder-inclusive, community-directed evolution of the field.

Synthetic Biology R&D: Revolutionising Biotechnology

Synthetic biology (see Glossary) is a young field that emerged from the convergence of biosciences, information technology, and engineering. Since its coinage, synthetic biology has evolved as an umbrella term, defined by a conceptual framework that aims toward the rational design of biological systems to attain useful products. This is sought through integrating engineering principles at the core of the R&D cycle and replacing ad hoc and serendipitous practices characteristic of traditional biotechnology [1]. This process results in a more reliable and robust industry, compatible with automation and scalability, while also upgrading its capabilities to carbon-neutral, simplified production systems, with a wider range of products [2].

Synthetic biology has become a global enterprise, expanding to 40 countries, with almost 700 organisations conducting synthetic biology research, funded by 530 funding agencies [3]. The promising breakthroughs and disruptive technological advances delivered by synthetic biology are evidence of the support of governments and funding bodies, who have also fostered programs that facilitate routes to market and the creation of a thriving heterogeneous community (Box 1) [4]. As a consequence, the scope of the biotech industry and its market has been revolutionised to a scale that required a new defining term: the **bioeconomy** [5].

Here, we adopt the OECD bioeconomy definition (the share of the economy delivered by biotechnology), although other definitions also include activities transforming bioresources. The bioeconomy is now included in economic roadmaps of many nations and regions, where synthetic biology is a key technology and an enabler of the global transition to a bio-based economy. This transition is proposed as the ultimate solution to sustainably fulfil the current and future food, health, and energy demands of a growing global population, where already-scarce natural resources are challenged by constrains of climate change [5].

Is There Really A Biotech Revolution? The Markets Say Yes

Current reports estimate that biotech had contributed US$324 billion to the US bioeconomy by 2012 [more than 2% of the US **gross domestic product** (GDP)], with an annual 10% growth over the past decade [6]. The European Union (EU) has estimated that its bioeconomy has a value of €2 trillion, although this figure includes activities beyond biotech [i]. Similarly, the UK has estimated its bioeconomy to be valued at £150 billion, predicting a growth of £40 billion over the next decade [ii].

Public and private biotech markets have also expanded, with the longest and largest expansion in biotech history beginning in 2009 and peaking in 2015. Since 2013, more than 224 companies launched on public markets with **initial public offerings** (IPOs), creating a market value of US $95 billion. This unprecedented period

Glossary

Bioeconomy: the application of biotechnology to primary production, health, and industry, where biotechnology contributes to a significant share of economic output.
Capital flow: movement of money for investment, trade, or business production, including investment capital, capital spending on operations, and R&D.
Compound annual growth rate (CAGR): mean annual growth rate of an investment over a specified period of time longer than 1 year.
Early-stage company: a company that is able to begin operations but is not yet at the stage of commercial manufacturing and sales. Early-stage financing supports a step-up in capabilities.
Equity: the value shares or stocks of the shares issued by a company that represent ownership interest. Equity financing is a method of raising capital by selling company stock to investors. In return for the investment, the shareholders receive ownership interests in the company.
Gross domestic product (GDP): an indicator of the economic performance of a country or region by measuring the market value of all final goods and services produced in a given period.
Initial public offering (IPO): the act of offering the stock of a company on a public stock exchange for the first time.
Innovation capital: cash raised by companies with revenues of less than US$500 million.
IPO window: a period with more than four IPOs per month, indicative of market strength.
Moore's law: a prediction made in in the field of integrated circuits, where the number of transistors in a chip will double every 2 years while maintaining the same price.
National Association of Securities Dealers Automated Quotations (NASDAQ) biotech index: a stock market index for NASDAQ-listed companies classified according to the Industry Classification Benchmark as either Biotechnology or Pharmaceuticals and also meeting other eligibility criteria. The NASDAQ index, founded in 1971, is an American stock exchange, the second largest in the world.
Pre-money valuations: the valuation of a company or asset before an investment or financing.
Seed funding: modest amounts of capital provided to entrepreneurs to finance the early development of a new product or service.
Synthetic biology: as defined by the European Commission, the engineering of complex biological systems with novel functions, done in a rational and systematic matter, at all levels of hierarchical structures (molecules, cells, tissues, and organs).
Venture capital (VC): private equity investment (not publicly traded in stock markets) from investors who seek stakes in start-up, small, and medium-sized companies with strong growth potential. These are, in general, high-risk/high-return opportunities.

Box 1. Turning **Synthetic Biology** into a Global Enterprise

Promising projects emerging during the mid-2000 s encouraged the launch of major EU and US federal initiatives (Figure I). Among them, in 2006, the National Science Foundation (NSF) funded US$40 million to initiate the Synthetic Biology Engineering Research Center (SynBERC), a multi-institutional research centre fast-tracking the commercialisation of synthetic biology products; since then, the NSF has allocated almost US$140 million to synthetic biology research [10]. The same year, after a presidential mandate to develop a biofuel economy, the US Department of Energy (DOE) announced a US$1 billion investment in a multi-institutional consortium to progress each stage of biofuel production (from basic research and enabling technologies to crops and microbes), with more than US$400 million allocated to synthetic biology related research [xxiv]. The US Government has invested between US$500 million and US$1 billion in synthetic biology research since 2005, with a marked 200% increase in 2010, when the US Defence Advanced Research Projects Agency (DARPA) launched the precursors of its Living Foundries ATCG and 1000 Molecules programs [xxv] to leverage bioengineering capabilities for manufacturing platforms. Likewise, the National Institute of Health (NIH) has funded more than US$50 million from 2005 to 2010 and US$20 million from 2014 to 2019 for the Genomes-to-Natural Products program [4]. Meanwhile, in the EU, a gross figure of €450 million in synthetic biology funding was reported from 2004 to 2013 [xxvi]. The UK began funding synthetic biology activities in 2007 and, since then, has become the world's second-most active nation in synthetic biology activities and the European leader, investing over £300 million in synthetic biology activities. Unlike the USA, UK synthetic biology programs have been developed under a unified strategy, as detailed in its roadmap, focussing on developing a robust research community with strong links to industry. In 2016, the UK developed a new strategic plan, 'BioDesign for the BioEconomy', aiming at higher impact for their synthetic biology market [2]. Overall, centres performing synthetic biology activities have been reported in 17 countries in Europe. On the other side of the world, China published its synthetic biology roadmap in 2010, allocating 260 million Yuan (US$36 million) per annum [10]. In 2016, the Human Genome Project–Write was launched with an initial budget of US$100 million, sourced from private and public organisations worldwide. However, its total cost is expected to exceed US$3 billion [13].

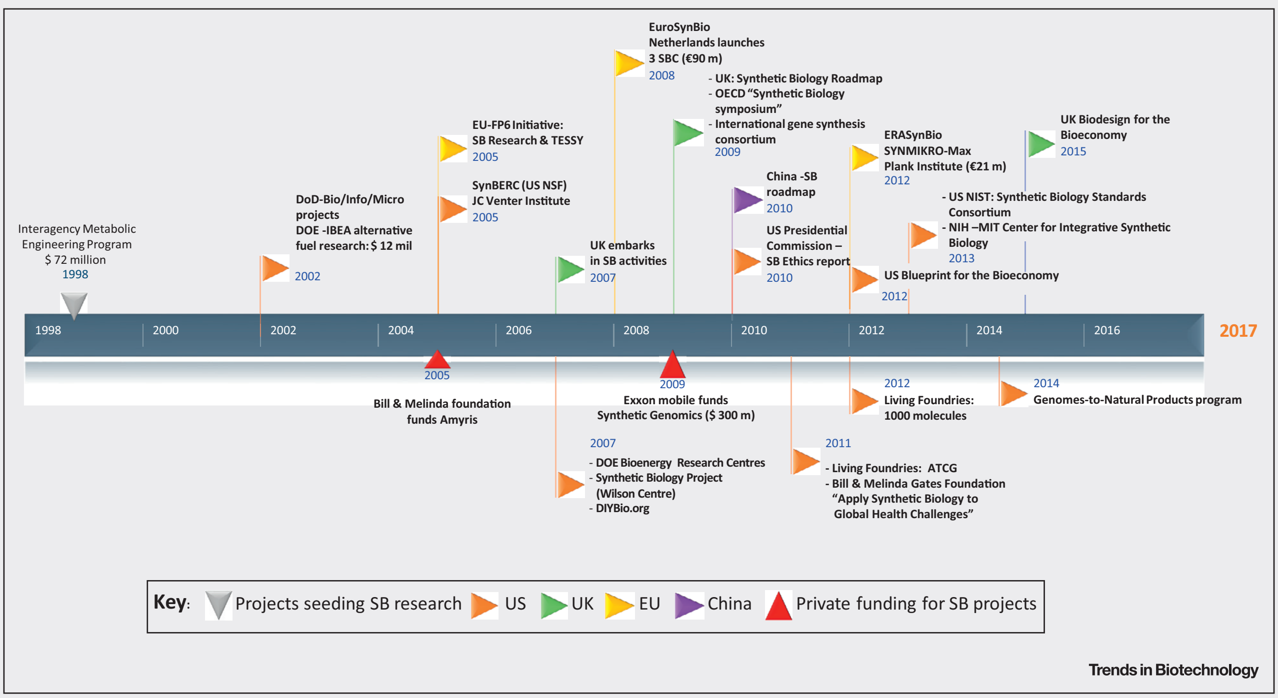

Figure I. Initiatives Driving Synthetic Biology Expansion and Its Adoption as an Industrial Technological Platform.

has defined the longest and most prolific **IPO window** in biotech history [7]. In 2015, biotech companies raised an unprecedented US$71 billion, with 58% (US$41.3 billion) corresponding to **innovation capital** (raised by companies with <US$500 million in revenues), featuring a record-high US$11.8 billion in **venture capital** (VC) funds (30%) and also a record-high US$3.5 billion in early-stage funding (235 series A and **seed fundings**) [8]. Despite the contraction of the market in 2016 (typical of the cyclic behaviour of the biotech market), the IPO window remained open, featuring a high proportion of **early-stage companies**, who raised 30% more than **pre-money valuations** [iii]. Similarly, venture funding of biotech remained strong, with US VC firms investing approximately US $7 billion (well above the US$4.2 billion historic average), while average start-up investment doubled from US$7.5 to US $15 million per deal [iv].

Overall, despite the volatility of the markets, the biotech industry has maintained a steady expansion, and the **National Association of Securities Dealers Automated Quotations (NASDAQ) biotech index** is still performing at 160% of its value 5 years ago. The industry is providing a rich pipeline of products, with high capitalisation among its players, higher flow of funds in the **equity** market (more IPOs than any other industry sector), and a larger participation

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of earlier-stage players, all of which is characteristic of a prolific industry [7].

Shaping the Bioeconomy

The Influence of Synthetic Biology on the Biotech Market and the Bioeconomy

Despite its youth, synthetic biology already has a significant market stake, being valued at US$3.9 billion in 2016, growing at a **compound annual growth rate** (CAGR) of 24.4%, and expected to reach approximately US$11.4 billion by 2021 [9]. However significant, this valuation is conservative because its contributions are not confined to any readily measured biotech industry segment but instead benefit the overall industry. Synthetic biology has expanded the biotech industry by enabling biotech to be integrated in other industries, such as DNA data archives [v] and nano-motors and molecular machines [vi] in the tech industry, attracting new players through easy-to-use and inexpensive tools (e.g., Amino Labs [vii] and Bento Labs [vii]), and enabling novel and sophisticated production systems and products. Overall, synthetic biology is an innovation platform driving the expansion of the bioeconomy; its contributions go beyond research and include the development of social and community-based initiatives facilitating its acceptance and integration by industry, society, governments, and markets [2,5,10].

Accelerating the R&D Cycle

The initiatives supporting synthetic biology prioritised the advancement of enabling technologies (Box 2), some of which have advanced the scope of numerous research areas in industry and academia, rendering a potential economic impact of between US$700 billion and US$1.6 trillion per year by 2025 [11]. Beyond these technological advancements, synthetic biology has transformed conventional R&D cycles (Figure 1) in the biotech industry by integrating the following approaches that improve reliability, speed, and costs: (i) *in silico* modelling (through abstraction) to reduce trial-and-error approaches; (ii) public repositories of standardised genetic components,

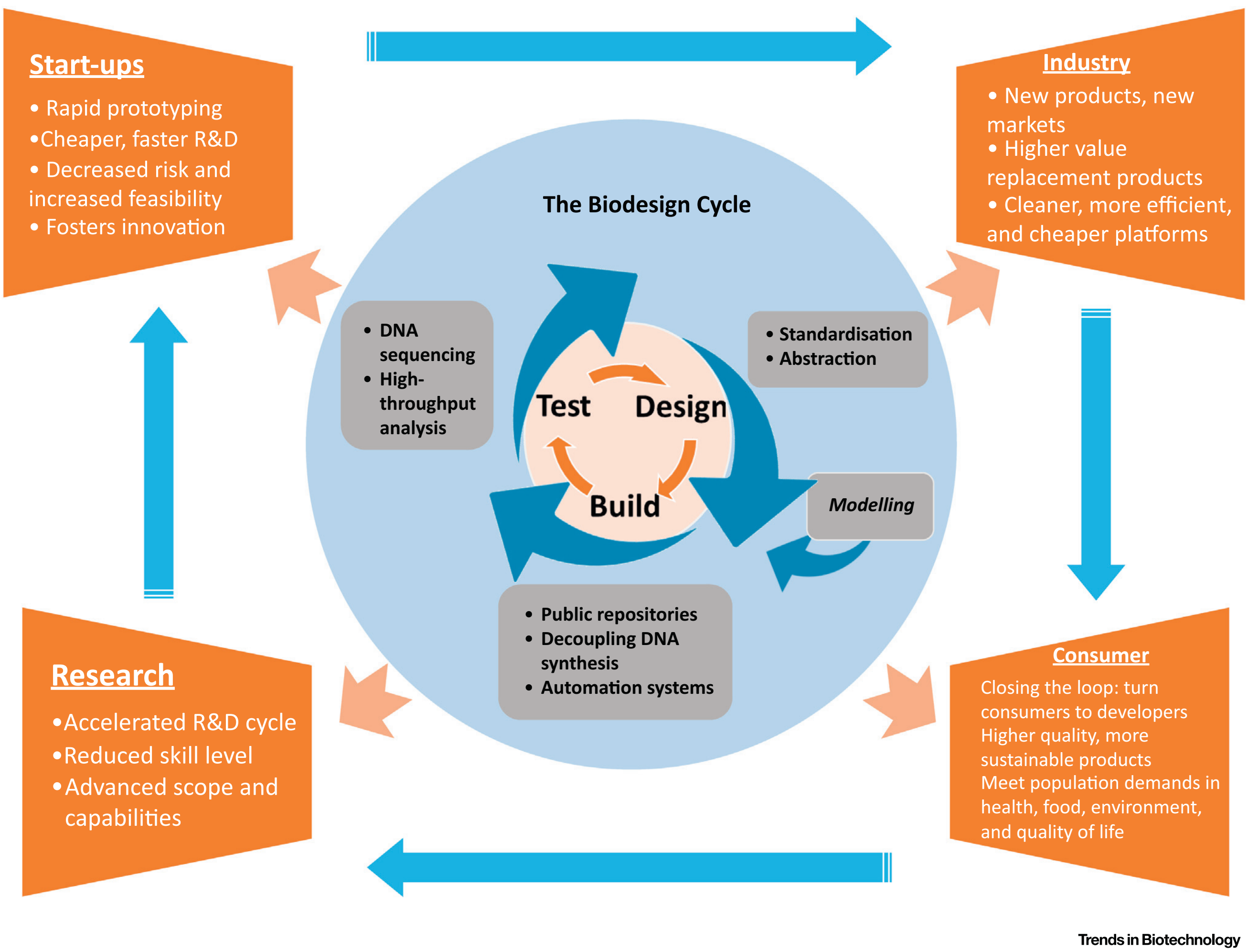

Figure 1. The Synthetic Biology Biodesign Cycle and Impacts on Stakeholder Groups in the Product Supply Chain.

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Box 2. Synthetic Biology Fosters Disruptive Technological Advances

DNA Sequencing

As an outcome of the thousand-dollar genome project, next-generation sequencing (NGS) and third-generation sequencing platforms were conceived (Figure I). These revolutionary technologies have increased productivity more than 500-fold, changing the sequencing economics and seeding an industry that since 2007 has outpaced **Moore's law**. These technologies have yielded a 10 000-fold price decrease for sequencing a human genome relative to the cost in 2004 [xxvii].

DNA Synthesis and Assembly

Over the past decade, traditional *de novo* DNA synthesis methods have been significantly improved, but the introduction of novel microchip-based DNA synthesis strategies has represented a truly disruptive technology in this industry, because it enables miniaturised, in-parallel, and automated production; increases throughput and efficiency; and increases productivity by more than 700-fold. These advances have facilitated the synthesis of gene-size DNA fragments and prompted a 10^4–10^6 decrease in the cost of oligonucleotide synthesis and a 100-fold decrease in the cost of gene synthesis. Assembly of longer DNA constructs (>2 Kb) is now possible through novel high-fidelity *in vitro* enzymatic assembly methods that are also inexpensive and suitable for automated systems [14].

Genomic Engineering

The advent of the CRISPR/Cas9 as a genome-editing technology in 2013 marked the beginning of a new genome-engineering era. Since 2013, CRISPR/Cas9 has proven effective in a multitude of organisms, including humans. Its superior efficacy and precision, coupled with its simplicity and low cost (<US$100), has revolutionised the genomic engineering arena and enabled its widespread adoption in research and industry by both trained scientists and amateurs [xxviii].

Mathematical Modelling

Modelling is an elementary tool for the rational design of robust and complex synthetic biology systems. It enables abstraction and increases the speed and reliability of building synthetic biological devices and systems by reducing the amount of time-consuming, expensive, and unpredictable wet-lab experiments. An increasing reliance on *in silico* models accelerates innovation and reduces costs [1].

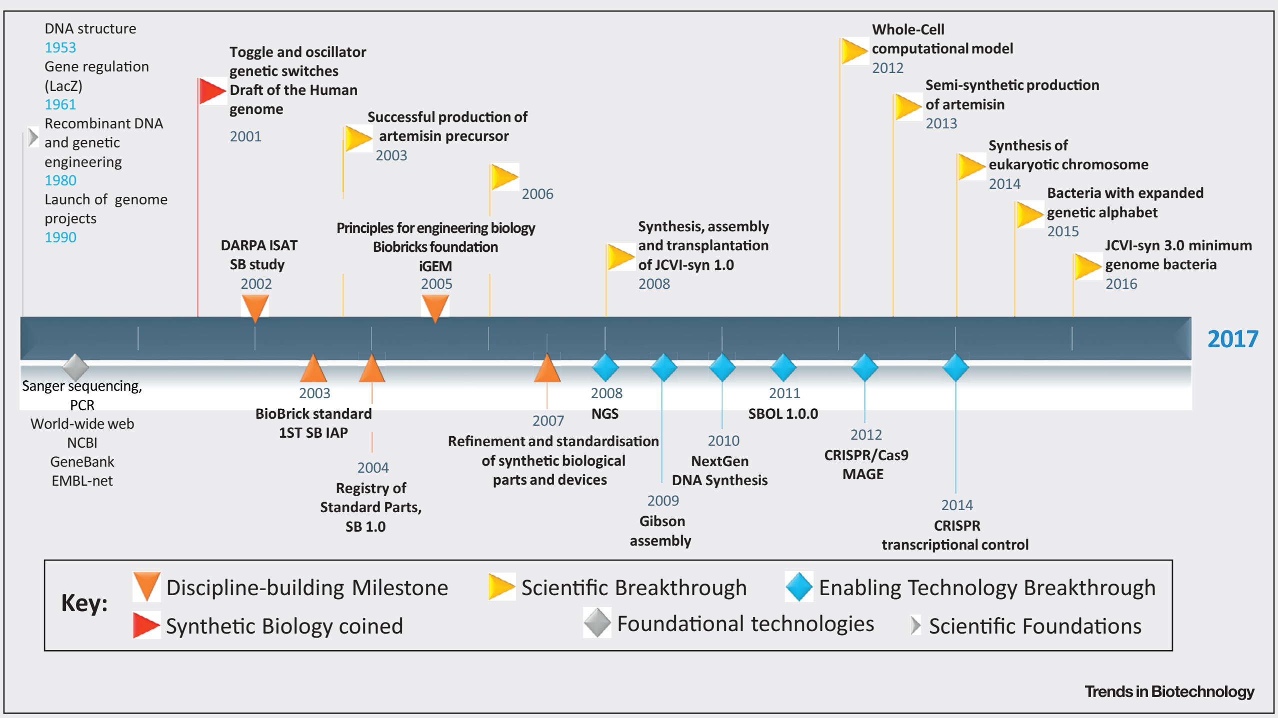

Figure I. Scientific Breakthroughs, Advances in Enabling Technologies, and Milestones that Have Built Synthetic Biology as a Discipline.

enabling sharing of parts that can be reused and optimised for different purposes [1,12]; (iii) decoupling R&D projects from manufacture (such as DNA synthesis), where research efforts and scaled manufacturing can be performed simultaneously by different entities [ix]; and (iv) automation and scaling [x]. This framework advances innovation by providing a common language and infrastructure encouraging collaboration, enabling in-parallel work, and reducing the dependence on highly trained specialists and expensive, time-consuming lab work [xi].

Fostering Investment and Entrepreneurship

By adopting this framework, biotech projects have become more reliable and feasible endeavours that are more attractive for investment. Biotech now has an extensive investor base comprising recognised investor firms, including renowned tech firms such as Google Ventures Appendix A[xii] and Y Combinator [xiii,xiv]. Synthetic biology has more than 20 dedicated business incubator programs (supported by industry, government, or VC firms), including LABS (Singularity University), and IndieBio and RebelBio (US and Ireland [xv]). The landscape of biotech investment has changed, with the marked increase in net **capital flow** and proportion of innovation and early-stage capital strongly supported by corporate VC firms, implying a structural change in the markets fostering entrepreneurship, as evidenced by funding raised by synthetic biology firms [xvi] [7,8]. Innovation is also promoted by increased accessibility and the numerous public-funded initiatives that recruit young talent to the field (from high-schoolers to university undergraduates) through community-building activities, such as LEAP [xvii], BioBuilder [xviii], and the iGEM competition [xix], which have trained over 25 000 students and have provided the workforce with key industry and entrepreneurship skills. These programs create an environment encouraging the generation and exchange of ideas that may develop into novel applications[xx].

Enabling New Products

The novelty fostered by these initiatives and the increased capabilities of its technological contributions have expanded the scope of synthetic biology far beyond traditional biotech-reliant industries. Novel products that were never previously considered are now emerging for less-saturated or less-restrictive markets, such as cosmetics, clothing, materials, nutrition, education, and others, with shorter R&D cycles accelerating the pace for launch to market[xxi]. Synthetic biology applications are conquering new markets and shaping the bioeconomy by integrating it with industry sectors that are not accounted for in traditional biotech. A 2016 survey reported over 350 synthetic biology dedicated firms across the USA and the EU (in 16 different industries) raising US$3.3 billion between 2009 and 2015. In 2016, 190 American synthetic biology companies raised US$830 million[xxii]. For a listing of companies, see [xxiii].

Replacing Traditional Industrial Processes

The technological advances brought by synthetic biology have enabled projects delivering high-value products in the traditional biotech sector. In the energy sector, synthetic biology has enabled the scalable production of biofuels and petroleum-derivative products, which use carbon-neutral feedstocks to improve sustainability and decrease ecological impact. In addition, the diagnostics industry has benefited from synthetic biology tools and has applied them to multiple novel molecular and/or microfluidics diagnostics platforms that are now revolutionising the industry. Synthetic biology has furthermore been adopted in the pharmaceutical industry, enabling drug discovery and the creation of more effective, safer, and cheaper drugs, and for vaccine development, because it reduces the time for development significantly. Finally, it has been adopted in various industries to replace older production methods for more efficient and cheaper production systems that are more sustainable and harmonious with the environment [6,9].

Concluding Remarks

It remains to be seen whether synthetic biology promises will be realised more than earlier biotech hopes. This community, from the outset, placed a great deal of attention on the bioeconomy (including product development needs, routes to market, etc.) to avoid the commercial failures observed with traditional biotech. The community-directed evolution approach of synthetic biology makes it unique, and increasing success stories may lead to future recognition of this 'way to do business' as a game changer in scientific technology development.

Resources

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