REVIEW
Life Research 2025;8(1):6. https://doi.org/10.53388/LR20250006

Prospects of synthetic biology in revolutionizing microbial synthesis and drug discovery

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Abstract

Synthetic biology (SynBio) is an emerging field of study with great potential in designing, engineering, and constructing new microbial synthetic cells that do not pre-exist in nature or re-engineering existing cells to accomplish industrial purposes. Systems biology seeks to understand biology at multiple dimensions, beginning with the molecular and cellular level and progressing to the tissues and organismal level and characterizes cells as complex information-processing systems. SynBio, on the other hand, toggles further and strives to develop and create its systems from scratch. SynBio is now applied in the development of novel therapeutic drugs for the prevention of human diseases, scale up industrial processes, and accomplish previously unfeasible industrial outcomes. This is made possible through significant breakthroughs in DNA sequencing and synthesis technology, as well as insights gained from synthetic chemistry and systems biology. SynBio technologies have allowed for the introduction of improved and synthetic metabolic functionalities in microorganisms to enable the synthesis of a range of pharmacologically-relevant compounds for pharmaceutical exploration. SynBio applications range from finding new ways to making industrial chemical synthesis processes more sustainable as well as the microbial synthesis of improved therapeutic modalities. Hence, this study underpins several innovations, auspicious potentials, and future directions afforded by SynBio that proposes improved industrial microbial synthesis for pharmaceutical exploration.

Keywords: synthetic biology; drug discovery; microbial synthesis; sustainable development; genetic circuit; gene editing

Author contributions

Ezeako EC conceptualized the literature review and designed the study. Ezeako EC, Itam YB, Solomon AY, Aham EC, Ogbonna CP, Amuzie NG, Aondover CD, and Osuagwu GO carried out background research and help in visualizations. Ezeako EC wrote the initial manuscript. Ozougwu VE, Ezike TC, and Ezeako EC reviewed and corrected the text. All authors have read and approved the manuscript.

Competing interests

The authors declare no conflicts of interest.

Acknowledgments

The authors wholeheartedly acknowledge the staff of the University of Nigeria, Nsukka for their solidarity and assistance during the study. The immense contributions of members of other institutions in the course of the study are very much appreciated.

Peer review information

Life Research thanks Kasamba Ilunga Eric and other anonymous reviewers for their contribution to the peer review of this paper.

Abbreviations

SynBio, synthetic biology; HTS, high-throughput screening.

Citation

Ezeako EC, Solomon AY, Itam YB, et al. Prospects of synthetic biology in revolutionizing microbial synthesis and drug discovery. *Life Res.* 2025;8(1):6. doi: 10.53388/LR20250006.

Executive editor: Yu-Tong Liu.

Received: 30 June 2024; **Revised:** 29 September 2024; **Accepted:** 30 December 2024; **Available online:** 06 January 2025.

Life Research 2025;8(1):6. https://doi.org/10.53388/LR20250006

Background

Synbiology coined from the term synthetic biology (SynBio) is a new-fangled multidisciplinary field of study that integrates principles from engineering, biology, and computer science to design and build innovative biological systems with enhanced functionalities, to help make feasible processes that were initially termed unfeasible with conventional approaches [1]. It has been proposed that synbiology will revolutionize how the engineering of biological systems is approached, conceptualized, and designed [2]. As an emerging area, the vision and applications of SynBio are expected to influence many other scientific and engineering fields, as well as other elements of society and daily life. SynBio is a comprehensive engineering and manipulation technique that goes beyond traditional genetic engineering [3]. SynBio is not just concerned with altering genetic material; it also produces complex artificial systems that modulate metabolic pathways or even reprogram entire organisms to manage their biological activities or pre-existing conditions [4]. SynBio shares some principles in common with systems biology via its emphasis on systems as opposed to individual genes or pathways, however, the main difference between the two concepts is that SynBio focuses on creating new and novel systems whereas system biology analyzes biological organisms in their entirety and rigidity [1]. Synthetic biologists design and build composite non-natural biological systems deploying the principles learned from systems biology and synthetic chemistry as well as sharing their perspectives holistically [5].

Drug discovery efforts are evolving as a result of the growing science of synbiology. Biological systems, particularly plants, have been the principal source of human medications for thousands of years [6]. The challenges in resynthesizing natural molecules, on the other hand, have repeatedly discouraged the pharmaceutical industry from harnessing this abundant source of human medicine [7]. The incorporation of genetic circuits engineering in drug discovery, particularly in the optimization of biosynthetic pathways, high-throughput screening (HTS), and easy synthesis of complex drugs highlights the efficiency and innovative contributions of synbiology in pharmaceutical exploration. Intriguingly, recent efforts in SynBio have enabled the optimized alterations of certain genes that control key microbial biosynthetic pathways, which has in turn made possible the in-depth study of the vast chemical space occupied by naturally-occurring compounds [6]. SynBio technology has shown remarkable potential to harness the stages of novel drug development targeted toward the effective management of myriads of human medical conditions [8, 9]. Recent advances in SynBio technology have been instrumental in the realization of long-term production of high-value pharmaceuticals, including antibiotics, antidiabetics, opioids, antimalaria, and anticancer agents [10, 11]. Interestingly, investigators are currently applying SynBio approaches to design SynBio-based production systems for the manufacturing of high-value bioproducts, including flavonoids, resveratrol, catechins, and isoprenoids [12]. Auspiciously, SynBio aims to expand and modify the normal characteristics of living organisms and design them to carry out novel tasks that were initially unfeasible. A summary of the concepts of SynBio technology and its auspicious prospects in microbial synthesis towards drug development is shown in Table 1.

Table 1 Overview of key concepts of SynBio technology in industrial microbial synthesis and drug discovery

SynBio concepts	Overview
Fabrics of SynBio	The emerging field, SynBio leverages concepts in biology, chemistry, engineering, and computer science to design and construct novel biological systems for a variety of applications, including drug discovery.
Innovations in SynBio technology	Innovations in SynBio tools like CRISPR-Cas9, biosensors, AI, and machine represents the key drivers for developing and optimizing novel biological systems with high precision for industrial and therapeutic applications.
SynBio applications in drug discovery	Utilization of SynBio concepts has aided the optimization of drug biosynthesis in microbial systems, affording efficient and sustainable development of therapeutic modalities like anticancer agents, antibiotics, and antimalaria drugs.
Underpinnings of genetic circuits	Similar to electronic circuits, genetic circuits are designed to control cellular behavior. Genetic circuits sense physico-chemical or molecular cues and respond by controlling and fine-tuning gene expression.
Genetic circuits in drug discovery	Genetic circuits have found interesting applications in high-throughput screening, biosynthetic pathways regulation, and targeted therapies. They have also displayed the capacity to be engineered to fine-tune microbial operations towards drug discovery.
Recent advances in drug discovery using SynBio	Recent advances in protein engineering, gene editing, genetic circuit engineering, optogenetics biosensing, and synthetic quorum sensing, have transformed drug discovery and development, making possible gene editing with high precision and the and use of biosensors for drug target validation and drug delivery mechanisms. Directed precursor biosynthesis has also revolutionized drug discovery as it allows the production of new or improved drug candidates from new substrates.
Future direction of SynBio-based drug development	Advances in CRSPR-Cas gene editing platforms will revolutionize SynBio-based drug development. The use of biofoundries (where machine learning intercepts genetic engineering) to design, create, and test genetically modified organisms. The use of omics analyses to test SynBio-inspired biological chassis for optimal bacteria factories.

SynBio, synthetic biology.

Conceptual framework of SynBio technology

The computer engineering-inspired hierarchical display (Figure 1) is one striking analogy that shows the conceptualization of both the aims and objectives of SynBio. From the hierarchical display, every constituent is rooted in a more intricate system that affords its context. Construction and implementation of new characteristics take place at the bottom but have the upper hierarchy in mind in a bottom-up approach. At the base of the ladder are fundamental building blocks, such as DNA, RNA, proteins, and metabolites (including nucleotides and amino acids, and carbohydrates and lipids), corresponding to the bodily layer of capacitors, resistors, and transistors found in the computer engineering. Next is the device layer, which consists of biochemical reactions that control information flow and regulate physical processes, similar to the computer-engineered logic gates that execute computations. The modular layer is where the Synbiologists assemble complex pathways that work collectively as integrated circuits using a broad range of library of biological devices. The linking of these several modules together as well as their insertion into host cells creates an avenue for the Synbiologists to modify or extend the characteristics of living cells in an intended manner [13]. Although separately operating cells could be engineered to execute certain tasks of diverse complexity, more complicated but coordinated tasks are possible with communicating cell populations, similar to computer networks.

Historical developments of SynBio technology

The inception of SynBio may be traced back to the 1960s when scientists initially began *in vitro* manipulation of DNA, which paved the way for the advent of recombinant DNA technologies. The development of recombinant DNA technology in the 1970s made it possible for researchers to alter the genome of microorganisms by deleting or inserting certain genes. This led to the engineering of the first genetically modified organism in the year 1975, where a microorganism that bears a foreign gene for antibiotic resistance was made [14]. Eventually, in the 1980s, further advancement of genetic engineering techniques led to the development of site-directed mutagenesis approach, which allows for specific modifications of DNA sequences. Consequently, human insulin production leveraging recombinant DNA technology became the foremost industrial application of genetic engineering, which was later approved for clinical use in 1982 [15]. Progressively, in the 1990s, the advancement of genetic engineering resulted in the quest to sequence the entire genomes of living organisms [16, 17]. Thereafter, the successful sequencing of the first bacterial genome in the year 1995 became a turning point in the field of genomics, which paved the way for scientists to study the entire genetic makeup of an organism, as well as correlate each gene with its functionalities [18]. Concurrently, the Human Genome Project started in 1990 and was successfully completed in April 2003, two years ahead of time scheduled and under budget, and was published in 2004; affording the scientific community with the ability to read the comprehensive genetic blueprint nature holds for mankind [19, 20].

Toggling further, in the early 2000s, SynBio emerged as an innovative approach to engineering cell biology. The core objective of SynBio was to open doors for the creation of novel biological systems with specialized properties previously unfeasible, by using engineering concepts and principles [21]. Strikingly, in the year 2000, the first synthetic gene was produced, which established the foundation for the concepts of SynBio. The earliest genetic circuits that humans built established the repressilator and the genetic toggle switch [22]. The discovery of the lac operon earlier in the short history of SynBio appeared to be the first time, scientists witnessed the possibility of a naturally occurring genetic circuit [23]. The target gene expression was toggled on and off by the genetic toggle switch. The repressilator oscillates similar to a clock with a circadian rhythm. These two findings demonstrated that mathematical principles may be used to create gene regulation networks [13]. Additionally, the first BioBrick parts and the BioBrick technical standard for bioparts were created by MIT researcher Tom Knight [24, 25]. Bioparts are biological system parts that are engineered to a certain technical specification. In this case, BioBricks inserts specific genetic sequences using restriction enzyme functionalities and stores this genetic code in a vector, in this case *E. coli* plasmids [26]. Additionally, large-scale synthesis of particular and increasingly complex DNA sequences was made possible by technological advances in DNA synthesis, which allowed scientists to create entire genomes from scratch. In 2010, a complete bacterial genome was synthesized and inserted into a different bacterial cell to create the first synthetic microbe [27].

Furthermore, the CRISPR-Cas9 technique, a cutting-edge and

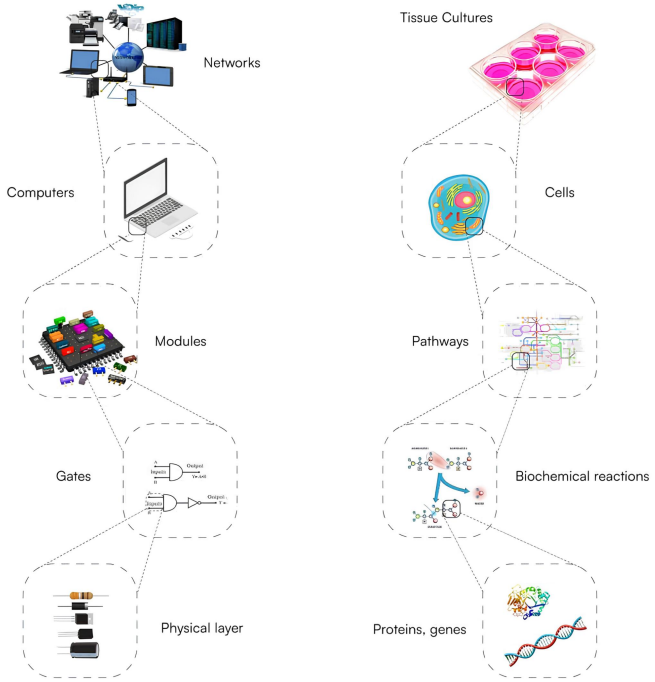

Figure 1 A hierarchical display of SynBio concepts similar to computer engineering. SynBio, synthetic biology.

valuable genetic engineering method that enables advanced gene editing, has substantially transformed the field of SynBio [28]. More specifically, the enormous advancements in SynBio have been made possible by the advent of computer-aided simulations and modeling of biological systems and processes. Currently, scientists can predict the properties of biological systems before they are developed, allowing researchers to create a more optimized version of biological systems [29]. Intriguingly, SynBio principles enhanced by recent advances in genome manipulations have found wide applications in several industrial processes for the realization of valuable products that benefit several facets of life endeavors, including, biotechnology, medicine, biodefense, and agriculture [1, 11, 30]. Moreover, the synthesis of highly revolutionizing drugs employed to treat the most severe and complicated diseases, such as cancer and genetic aberrations, as well as the realization of drought-resistant and medicinal plants, and microorganisms with improved biosynthetic amenabilities, have seen massive and progressive feasibility with the deployment of SynBio-based technology [31].

Application of SynBio technology in drug discovery

Genetic circuits engineering

Genetic circuits, akin to electronic circuits utilized in computers systems, are designed to process information and execute certain tasks within biological systems [32]. Similar to the architecture of electronic circuits that comprises of a network of components, such as switches, transistors, and resistors that control electrical signals, genetic circuits are made up of genes, promoters, and regulatory elements that coordinate the flow of molecular signals within the cell [33]. These biological circuits respond to specific biological and physico-chemical inputs, such as molecular cues, light or temperature and produce an output in form of gene activation or the production of specific protein, allowing for the control of cellular behavior with high precision [34]. Notably, integration of synthetic DNA sequences, which act as switches, similar to computer logic gates is employed in the fabrication of genetic circuits [35]. These genetic circuits could be engineered to respond to a variety of physico-chemical stimuli. For example, an inducer molecule may trigger a genetic switch that represses or activates the expression of a target gene, enabling the dynamic regulation of its cellular functions [36].

With recent advances in molecular biology, protein engineering, and the advent of more advanced genome editing tools, such as CRISPR-Cas9, researchers have concentrated on developing biological devices that can elicit certain phenotypic responses to certain input signals, such as light or molecular cues (Figure 2) [37]. For more than a decade, pharmaceutical research has adopted the use of SynBio-inspired genetic circuit, design not just to support the various stages of drug discovery but also to enable bioproduction of pharmaceuticals in microorganisms, serving as biofactories [8]. Essentially, a standard synthetic cell consists of three components: an inducer, which can be a small molecule, a ligand for a membrane receptor, or light (Figure 2A). These elements activate a genetically designed circuit (Figure 2B), with circuit induction leading to an output signal detectable by a light-emitting reporter gene (Figure 2C).

Genetic circuits in drug discovery

Application of genetic circuit engineering in drug discovery has avail tremendous and unprecedented possibilities in testing, screening, and synthesis of therapeutic compounds with high precision. Besides, the programmability of genetic circuits has made it a quintessential element of SynBio technology, particularly for pharmaceutical explorations [38]. Of note is its application in HTS, where synthetic cells equipped with genetic circuits acts as biosensors. SynBio-inspired artificial cells are programed in such a way that the elicit detectable signal, such as fluorescence, when they come in contact with a potential drug lead that could bind with a target protein [39]. This advances hold promises and has enabled researchers to rapidly identify promising bioactive lead compounds at reduced cost and resource expenditure and at the shortest time frame compared to traditional paradigms. For example, Ayon [40] used rapid and high-throughput screening of natural products and synthetic chemical libraries to develop antibacterial drug candidates. Besides, genetic circuits have allowed for dynamic fine-tuning of microbial biosynthetic pathways leading to drug development and synthesis [41]. Presently, it is now feasible to optimize the production of complex natural products, including anticancer agents, antibiotics, or hormones by re-engineering the genetic circuits and enzyme cocktails in microorganisms [42]. The ability to precisely control metabolic flux by incorporating synthetic genetic circuits into biological systems has translated into several breakthroughs, including the sustainable manufacturing of valuable drugs like artemisinin (a potent antimalarial candidate), some isoprenoids and amino acids, and several antibiotics at industrial bioproduction scale (5–50 g/L) [43]. Isoprenoids, polyketides, non-ribosomal peptides, and other naturally occurring polyphenols (stilbenoids, flavonoids) are the most common classes of natural products bioproduced via SynBio-based approach [8]. Besides, the plethora of data emanating from chemical proteomic studies has depicted the existence of many biological targets for a single drug [44]. This has propagated a holistic and systemic perspective of polypharmacology that is perfectly consistent with SynBio-inspired cell-based phenotypic and all-inclusive strategies.

Transformative potentials of synbiology on drug development

SynBio has exerted enormous impact on the drug discovery value chain, as well as the development and manufacturing phases of drugs. The decreasing cost of synthetic DNA, heightened and detailed knowledge of the genome, its organization, gene regulation, and the availability of host model organisms have aided in the realization of SynBio's achievements thus far and its future possibilities [45]. In addition, CRISPR-Cas research is growing, with significant implications for target identification and validation [46]. For instance, CRISPR-Cas9 editing platform is projected to cutdown the production of cell-line and animal models, promote the establishment of activity-dead mutations in target validation studies, and unearthing new collection of targets across therapeutic confines [47].

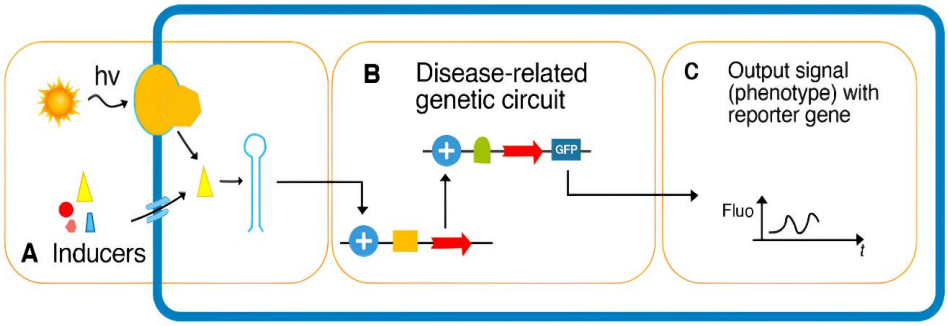

Figure 2 Basic components of standard synthetic cell. (A) Gene expression inducers such light (hv), drugs, cell messengers, nutrient, and other small molecules. (B) Gene circuit to regulate the expression of certain genes. (C) Reporter genes to regulate output signals associated with a disease phenotype.

The invention of assays, which are the foundation of the modern drug discovery process, owes a lot to SynBio and the engineering of biological circuits [48]. In spite of the recent breakthrough and advances in SynBio techniques, coupled with the increased availability of genetic sequences, and cutting-edge genome mining, the scientific community has witnessed tremendous upsurge in the commercial development of medicinal and pharmaceutical products from natural sources. Consequently, this has aided the design of improved therapeutic modalities, learning from natural phytochemical templates to tackle "hard-to-drug" targets such as protein-protein interactions and phosphatases, which may not be efficiently capture using conventional hit screening engines like HTS, DNA-encoded libraries, and fragment-based lead mining [49]. Combinatorial biosynthesis involving the permutation of biosynthetic gene clusters components are now employed to heighten the superiority of biosynthetic diversification without resorting to hard chemical synthesis [45]. For instance, deploying combinatorial biosynthesis, Thykaer et al. [50] modified cyanobactin ribosomal peptide natural product pathway to include non-proteinogenic amino acids and multiple tandem mutations in *E. coli.* The application of machine learning and artificial intelligence is also projected to improve BGCs remodeling and upgrade the likelihood of generating newer biomolecules [51].

Furthermore, the application of directed evolution has propelled a palpable improvement in the development of antibodies. Directed evolution couples genetically encoded libraries, gene variations, and selection pressure to improve antibodies development [52]. This powerful tool harnesses natural evolution to engineer protein structure and functions within a shorter timeframe, enabling the quick selection of variants of biomolecules with specific properties that is suitable for a given application [40]. Coupling to biological circuits has enabled *in vivo* directed evolution for drug discovery as well as the expression of new proteins with unique functionalities, such as enzymes capable of catalyzing new transformations in drug discovery and green chemistry in large-scale drug synthesis [45]. While modified enzymes are being utilized in discrete phases in bulk drug manufacturing, entire pathways for biosynthetic production can be designed [53]. While stepwise directed evolution has gained success, continuous directed evolution allows for many more generations to be studied, allowing for a deeper search through structure-activity space [52].

SynBio is spearheading the majority of advancements in cell therapy. These advances have already been demonstrated in oncology with palpable feats using chimeric antigen receptor T cells [54]. Also, SynBio has shown promising potential in a number of other areas, including cell reprogramming, precise genome editing to fix genetic abnormalities, and the reengineering of cells and tissues in regenerative medicine [55]. Also, synthetic cells can now be design to sense their surroundings and behave in an intended manner to treat acute and chronic disorders [11]. Besides, workflows combining modern technologies such as artificial intelligence and machine learning with SynBio and chemistry are emerging to push the boundaries of drug development even further [45]. SynBio undoubtedly has an impact on all stages of drug discovery and development, and acknowledging the discipline's contribution can increase the prospects for impact on the drug research and development value chain. The contribution of SynBio concepts in drug discovery processes is illustrated in Figure 3.

Emerging frontiers in SynBio-Inspired drug discovery and development

Targeted therapies and real-time control

The development of targeted therapies is another revolutionary breakeven that has been achieved via the construction of genetic circuits in biological systems [56]. Genetic circuits could be fabricated to sense a particular culprit biomarker of a given disease and induce the expression of genes that elicit therapeutic effect selectively on diseased cells, sparing healthy cells. This approach holds particular promise in cancer treatment, where genetic circuits engineered into immune cells (such as CAR-T cells) could recognize tumor-specific antigens and selectively target and destroy malignant cells amidst healthy ones [57]. Interestingly, genetic circuits are able to incorporate real-time control mechanisms. Researcher now design genetic circuits with self-regulatory properties, akin to feedback loops in electronic systems [58]. Thus, at certain threshold concentration of a target gene products, the circuit could automatically downregulate its production, allowing the drug levels remain within therapeutic windows and curtailing adverse off-target effects. Recently, Carneiro et al. [59] submitted a comprehensive review on the therapeutic applications of synthetic genes and genetic circuits. SynBio-inspired cell-based therapies integrating therapeutic gene circuits for on-demand restoration of homeostatic regulations hold huge prospects in the medical industry. The disease-control characteristics of artificial genetic circuits include disease prevention and diagnosis with or without the ensuing activation of autonomously controlled therapeutic actions [60].

Rational-based genetic design and drug biosynthesis

The paradigm of fabricating synthetic gene circuits for drugs biosynthesis utilized in Synbiology is analogous to medicinal chemistry rational-based drug design [8]. A significant finding in the 1990s established rational-based genomic design as a viable drug development technique. Secondary metabolites are produced by microorganisms, fungus, plants and other living organisms by the use of massive biosynthetic mechanisms [61]. These enzymatic modules can be combined in synthetic cells to create novel natural products derivatives [62]. The initial use of Synbiology in drug development was purposed to promote innovative fabrication of novel chemical scaffolds with characteristics comparable to known natural products-derived human medications, increasing the possibility of eliciting superior potency and having the precise pharmacological activities [63]. The integration of these constituents can vary for different drug discovery applications, as illustrated in Figure 4A–D. For example, gene circuits from secondary metabolisms or cryptic biosynthetic units of microorganisms could be incorporated into host organisms to upregulate the expression of gene that code for the target compound (Figure 4A) or rearrange modules within biosynthetic units for exploring the chemical space of natural products (Figure 4B). Protein engineering is a SynBio tool used to explore the chemical

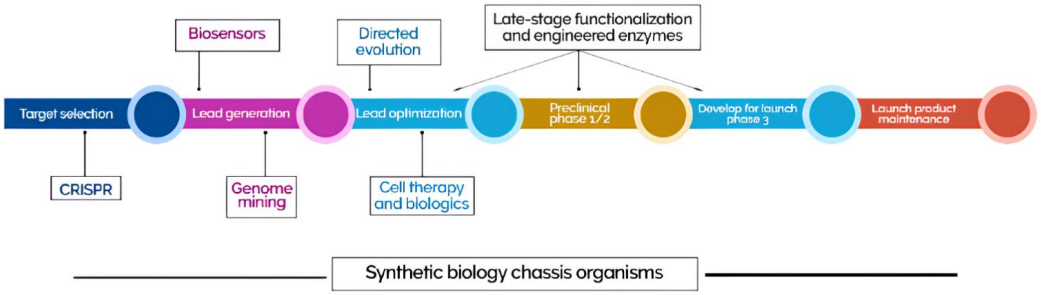

Figure 3 The contribution of SynBio concepts in drug discovery processes. SynBio, synthetic biology.

diversity of natural products [64]. Synthetically engineered pathways are usually inefficient and requires protein engineering and directed evolution to improve the efficiency [65]. Here, enzyme specificity is modified by introducing mutations in a single amino acid located at the binding site [66]. Substrate analogs are utilized to induce mutation on the selected enzyme to establish enzyme substrate promiscuity either towards directed precursor biosynthesis or mutational biosynthesis [67]. The orientation of enzymatic modules is modified using alternating spliced isoforms. Besides, site-directed mutagenesis can enhance the regio- or stereospecificity of an enzyme, increase the binding affinity of a chosen ligand, or select between enzyme isoforms [68]. Optogenetics, which involves the optical disruption and monitoring of physiological processes, has various characteristics that make it a viable tool for drug development [69]. Optogenetics integrates optical and genetic innovations to achieve targeted loss or gain of functionalities of spatio-temporally established events in individual cells or living systems (Figure 4C). Interestingly, optical assays operate at low cost and high throughput [70]. By principle, light can activate the expression of specific receptors, such as the bacterial enzymatic light-emission system encoded by the lux operon, protein photosensors like light, oxygen, or voltage domains, or green fluorescent protein. These biosensors have diverse applications, including validating drug targets, understanding the mechanism of action of a given drug through a designed disease model, and inducing a drug delivery mechanism at a specific site or under specific conditions [71]. Drug absorption, distribution, metabolism, excretion, and toxicity, represent a pivotal and determining factor in drug discovery and development efforts [72]. A potent drug option should exhibit satisfactory efficacy against the druggable target, as well as demonstrate excellent ADMET properties at a given therapeutic dose [73] Synthetic quorum sensing can be employed to investigate antibiotic persistence or resistance mechanisms in bacterial populations by altering the cell–cell communication system (Figure 4D). The QS is a bacterial cell-to-cell communication cascade that is dependent on the density of the bacterial population [74]. It entails small diffusible signaling molecular entities that stimulate the expression of several genes that control a wide range of biological functions. A dense colony population usually can create enough small molecular cues to upregulate a range of downstream cellular processes, including virulence and drug resistance mechanisms, antibiotics tolerance, and endanger the host [75, 76].

Directed precursor biosynthesis

Directed precursor biosynthesis is another SynBio-based drug discovery approach, where an enzyme is mutated through selection pressure with imposed substrates, and mutational biosynthesis or muta-synthesis, where the wild-type enzymatic pathway is disrupted by mutation, forcing supplemented substrate analogs to be processed by the enzyme through selective evolution [77, 78]. This process has open new possibilities for the optimization biosynthetic pathways for complex drugs production, that are inherently difficult to chemically synthesize. A typical example of directed precursor biosynthesis, is the use of mutational biosynthesis or muta-synthesis to produce analogs of existing lead compounds or entirely new pharmacologically-relevant molecule by compelling the enzyme to catalyze novel precursors [79]. These strategies have enabled the production of drugs other therapeutic modalities with unprecedent precision, efficiency, and less side effects. Recently, Hennrich et al. [80] in their study utilized biotransformation-coupled mutasynthesis strategy targeting phenylglycine residue to generate novel pristinamycin derivatives. Huo [81] also reported the precursor-directed biosynthesis and mutasynthesis of novel and potent derivatives of cinnabaramides and bottromycins from different *Streptomyces* strains, with fascinating antibiotic properties. Exploring the combinatorial biosynthesis of new analogs of erythromycin, McKenzie et al. [82] employed precursor-directed biosynthesis to generate a novel class of alkenyl- and alkynyl-substituted macrolides with properties akin to parent compound. Another study by Khoshbakht et al. [78] in attempt to distort the aniline moiety in vorinostat precursor and expand the chemical diversity of chalaniline A structures, carried out precursor-directed biosynthesis of novel chalanilines A moieties (aminofulvenes) from the fungus *Chalara sp* culture [83] (Figure 5).

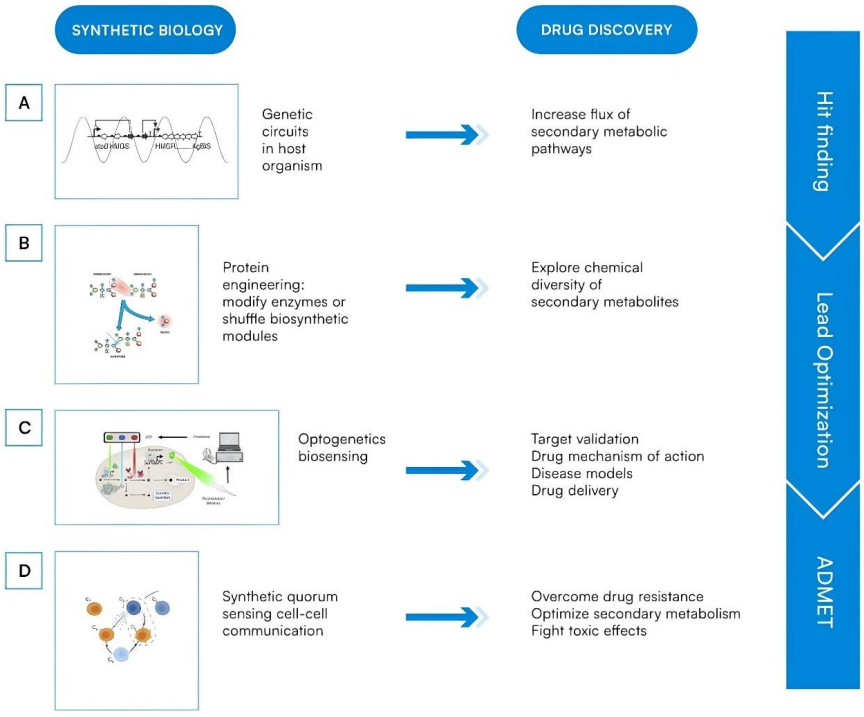

Figure 4 Application of SynBio techniques in various steps of drug discovery. SynBio, synthetic biology.

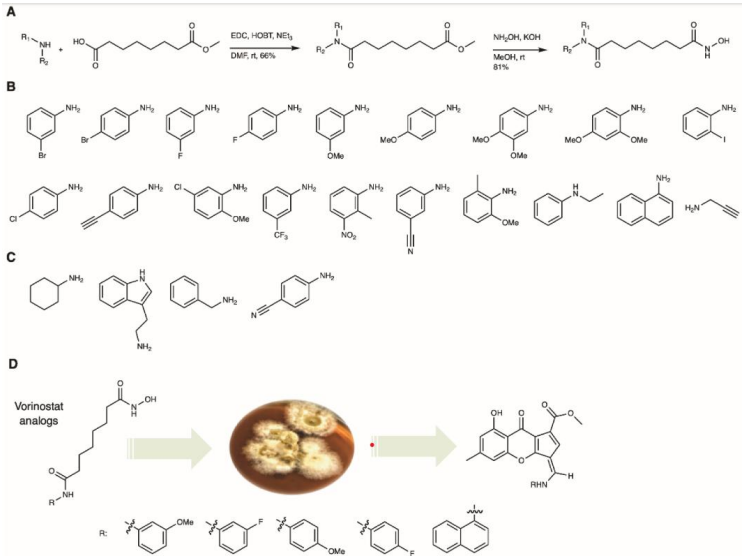

Figure 5 Stepwise preparation of vorinostat analogs and precursor-directed biosynthesis of novel chalanilines. (A) Synthesis of 33 analogs of vorinostat (R1 and R2 representing different substituents of the amine). Reproduced with permission. Soli ED, Braun MP. Synthesis of [phenyl-U-14C]aryl and [8-14C]carboxy labeled tracers of vorinostat. *J Label Compd Radiopharm*. 2006;49(5):437–443. Copyright 2006, Wiley. (B) biotransformation of a total of 19 amines into chalaniline A molecules. (C) The fungus was unable to incorporate 4 amine moieties. (D) Outline of precursor-directed biosynthesis of chalaniline A-type structures via the augmentation of vorinostat analogs into *Chalara* sp. cultures. Reproduced with permission. Khoshbakht M, Srey J, Adpressa DA, Jagels A, Loesgen S. Precursor-Directed Biosynthesis of Aminofulvenes: New Chalanilines from Endophytic Fungus *Chalara* sp. *Molecules*. 2021;26(15):4418. Copyright 2021, MDPI.

Future direction of SynBio technology in industrial processes

Innovations in SynBio technology are projected to open doors for several opportunities and scientific breakthroughs in the development of optimized microbial systems or the repurposing of existing cellular entities with improved functionalities [84, 11]. It is on this premise that El Karoui et al. [5] define SynBio as a disruptive industrial strategy at the heart of Bioeconomy, possessing the potential to proffer better solutions to the world's most pressing issues, including industrial production bottlenecks, agricultural challenges, environmental degradation, and healthcare issues. SynBio is an emerging and innovative discipline that continuously introduces novel approaches and strategies to solving herculean tasks. Advances in CRISPR-Cas9 genome editing tools have also facilitated a plethora of SynBio applications for the precise redesigning of microbial genomes [28]. Innovation in biosensors technologies is allowing for real-time monitoring and regulation of biological systems, paving the way for more exact and efficient exploitation of synthetic biological platforms [85]. The advancement in artificial intelligence and machine learning is tremendously transforming the building and improving synbiological systems. Currently, the use of algorithms to forecast and remodel certain characteristics of biological systems has enabled synbiologists to construct and improve biological systems for optimum efficacy and effectiveness [86]. Although, SynBio research focuses on genetic engineering, recently, advances in SynBio studies have been tailored towards the exploration of non-genetic biomolecular systems potential such as utilizing RNA functionalities in gene regulation and synthetic protein networks for processing information [1]. In addition, research to automate and couple machine learning with the design-build-test-learn cycle of synbiology to enhance performance is underway [84]. Biofoundries, an integrated molecular biology modality that allow for the rapid design, fabrication, and testing of genetically engineered organisms for biotechnological exploration is projected to host the design of next-generation cell biofactories and this SynBio-inspired biological chasis will be driven by multi-omic methodologies towards optimal microbial factories [87–89].

Conclusion

The concepts SynBio draws from the principles of biology, chemistry, computer science, and engineering to design and develop novel biological systems with improved and enhanced functionalities. Recently, this technology has shown enormous prospects in revolutionizing industrial microbial processes and the healthcare sector. SynBio has allowed for the development of improved novel and sustainable methods for the production of value-added biochemicals and therapeutic modalities using engineered microbes with reprogrammed enzymatic and metabolic functionalities. SynBio technologies has enabled the construction of genetic circuits for industrial applications. The integration of genetic circuits engineering in drug discovery, particularly in the optimization of biosynthetic pathways, HTS, and easy synthesis of complex drug leads highlights the innovation of SynBio technology in the pharmaceutical industry. It is now feasible to construct synthetic gene circuits to provide precise control over therapeutic interventions leading to personalized gene therapies that are tailored specifically to address an individual patient health condition, improving therapeutic efficacy while reducing adverse side effects. Akin to sensitive biosensors, gene circuits are able to deliver real-time therapy by precisely tracking numerous biomarkers or infections and inducing the synthesis of therapeutic modalities. The complicated maintenance of physiological homeostasis is linked to gene circuits'sensing and self-regulation abilities. The biosensing and self-regulating capacity of synthetic gene circuits correlates with the complex homeostatic regulation that occurs in the living system.

Looking forward, with the continuous advancements in artificial intelligence, machine learning, and directed evolution expanding the confines of innovation, the prospects of SynBio in microbial synthesis and drug discovery might know no bound. These advances will progressively refine and accelerate the process of drug discovery, affording better therapeutic options for addressing complex diseases with precision-engineered therapeutic modalities. As SynBio-based technology evolve, its overall impact on the health industry, particularly in personalized medicine and regenerative medicine, and its general pharmaceutical landscape will peak, affording hope for the treatment of hitherto untreatable diseases.

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