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# SYNTHETIC BIOLOGY STRATEGIES FOR DRUG DISCOVERY

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## ABSTRACT

The landscape of pharmaceutical research is undergoing a fundamental shift driven by the integration of synthetic biology (SB). Rather than relying solely on traditional chemical synthesis or the direct extraction of natural products, this discipline treats biological systems as programmable entities. By applying rigorous engineering principles to modify organisms, researchers can now design specific therapeutic outcomes and overcome long-standing barriers in drug development. This approach is currently transforming every phase of the lifecycle-from the identification of novel targets and the validation of disease models to the large-scale manufacturing of complex molecules through metabolic engineering and CRISPR-Cas9 technologies. Furthermore, SB facilitates the exploration of chemical diversity via late-stage functionalization and the biosynthesis of natural product analogs in genetically tractable hosts. This review explores the systematic application of SB to improve the speed, cost-efficiency, and quality of drug discovery, highlighting its potential to revitalize the pharmaceutical industry's focus on complex biological scaffolds and personalized medicine.

**KEYWORDS:** Synthetic Biology, Metabolic Engineering, CRISPR-Cas9, Drug Discovery, Late - stage functionalization.

## INTRODUCTION

In 1910, Stephane Le Duc proposed the concept of synthetic biology. Synthetic biology is an application of principles of engineering to the construction of life in a systematic way. Nature has been providing us drugs for thousands of years. But due to the difficulty in large-scale

production of these natural products (NPs) the pharmaceutical industries have abandon the source of natural medicinal products. The production can be favoured if these compounds are biosynthesized from source organisms to genetically friendlier hosts. Speed, cost, and quality are the fundamental systems which control the productivity of the pharmaceutical industries. These three critical elements have been improved for the effectiveness of drug discovery by applying the tools from synthetic biology. The first application of SB in Drug discovery was to innovate new chemical scaffolds having properties similar to that of well-known NP-derived human medicines, increasing the chance of being bioactive with the right pharmacological properties. The two of the most exciting fields for synthetic biology, cell therapy and genetic reprogramming, have been combined within immuno-oncology to produce one of the most novel medical approaches, using chimeric Antigen receptor T cells (CAR-T cells).

**Some basic ideas of synthetic biology**

A typical synthetic cell has three main parts: an inducer like a small molecule, a ligand that binds to a membrane receptor, or light that starts a newly designed genetic circuit. When this circuit is turned on, it sends out a signal that can be detected by a light-emitting reporter gene. These three parts can be combined in different ways depending on what the application is in drug discovery. Genetic circuits from secondary metabolism or hidden biosynthetic parts in microorganisms can be added to host microbes to help make specific compounds or mix different parts of biosynthetic pathways to explore new chemical possibilities. Light can also turn on the expression of certain receptors, like the bacterial system that makes light, known as the lux operon, or light-sensitive proteins like the LOV domain or green fluorescent protein. These biosensors can be used in many ways, such as checking if a drug target is working, understanding how a drug affects a disease, or delivering a drug to a specific place or under certain conditions.

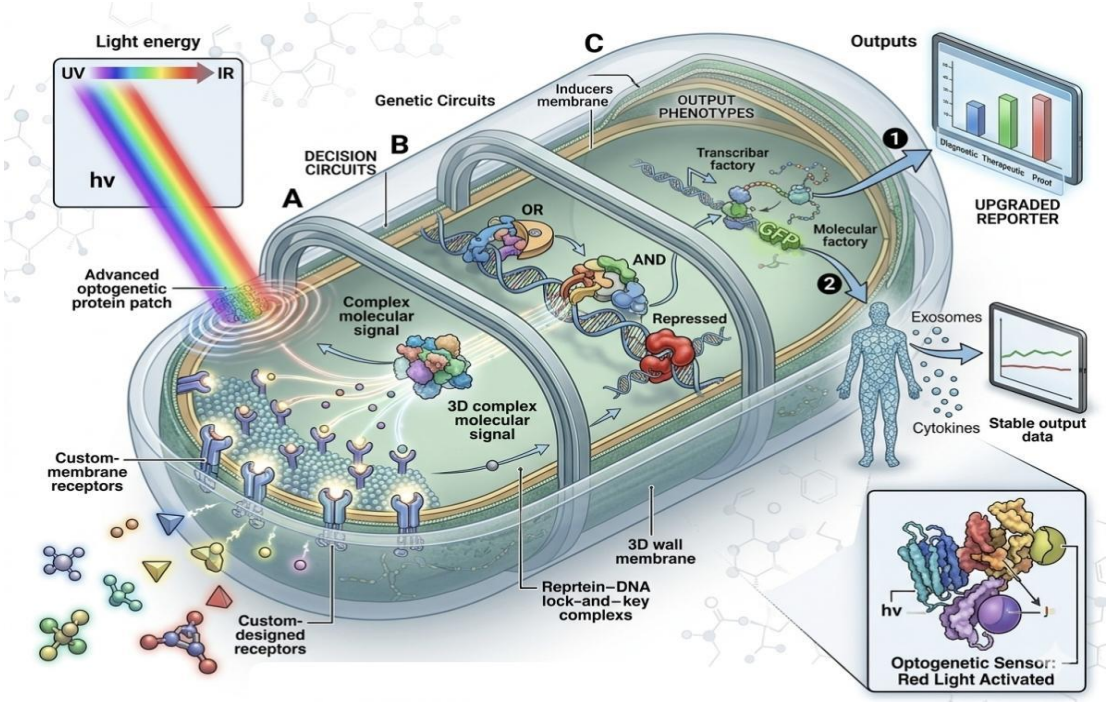


**Fig. 1: Synthetic Biology Circuit for Drug Discovery.**[20]

Synthetic quorum sensing helps study how bacteria resist or survive antibiotics by changing the way they communicate with each other. Protein engineering is another part of synthetic biology. By changing specific parts of a protein, scientists can make enzymes more precise in their actions, improve how well a molecule binds to a protein, or choose between different versions of an enzyme. Other techniques, not shown in the figure, include methods like directed precursor biosynthesis where enzymes are changed by exposing them to certain substances, or mutational biosynthesis where the normal pathway is stopped so the enzyme works with modified molecules through evolution.

**The rise of synthetic biology in drug discovery has a long history**

Modern pharmacology finds its roots in the early 20$^{th}$-century visions of Paul Ehrlich, who conceptualized ‘magic bullets’—compounds capable of precisely neutralizing pathogens without damaging the host. While the pharmaceutical ‘golden age’ successfully realized this through high-throughput screening and combinatorial chemistry, synthetic biology is now evolving this concept. We are moving from a ‘one-drug, one-target’ model toward a more sophisticated ‘network pharmacology,’ where engineered cells can process multiple signals to deliver multifaceted therapeutic responses.

At the start of the last century, there was a big breakthrough in solid and liquid phase synthesis. Combinatorial chemistry allowed scientists to explore new areas of chemical space

by changing known chemical structures in a controlled way. Combined with smaller biochemical tests, this made it possible to screen large libraries of chemicals for how well they bind to a specific target. Before proving this method's success, the pharmaceutical industry stopped most of its natural product research and focused on high-throughput screening to find initial drug leads.

The success of this approach depends on the quality of the compound libraries used. To increase the chances of finding useful drugs, scientists selected libraries with a wide range of chemical diversity and optimized their physical and chemical properties, like solubility and how easily they pass through cell membranes. With more information on the target molecule, they added more rules during the optimization to create libraries focused on specific targets.

This brings up another issue: the specificity of the compounds. A compound must be able to bind to one target without affecting others. If it binds to similar targets, it can cause harmful effects. This can happen when targeting a specific type of large protein family, like kinases. To improve the selectivity of drug candidates, industry and academic research centers developed high-throughput biochemical tests to check how different compounds interact with multiple family members of a protein. This led to chemical proteomics data showing that even selective drugs can bind to more than one target. This has changed the view of pharmacology from Paul Ehrlich's idea of "one drug, one target" to a more complex idea involving multiple targets, which can be managed by using drug combinations that work together.

Synthetic biology tries to understand this complexity by using an engineering approach to design biological systems, like synthetic cells or cell-free systems that respond to controlled signals.

In drug discovery, these systems help trigger the production of compounds from biosynthetic units, making it possible to explore a wide range of chemical structures. In- cell synthesis uses natural evolution to create molecules that work well in a living environment, which is helpful in the process of choosing the best drug candidates. Genome editing tools allow scientists to track the effects of specific signals through reporter genes, which is useful for confirming drug targets or disease models. This "rational-based biosynthetic drug design" approach offers a new way to create drugs based on scientific knowledge, similar to how drugs were designed in the past using rational methods.

Plants have been used for thousands of years not just for medicine and insecticides but also for colors, flavors, and scents. Because they can't move from one place to another, they've developed strong defense systems and the ability to adapt. As a result, they produce a huge variety of secondary metabolites that help them defend against diseases, insects, and environmental stress like UV radiation.

**Plants have some unique features that make them interesting for synthetic biology**

One of them is their ability to use a photosynthetic system to turn sunlight into organic compounds. This ability is also found in other organisms like cyanobacteria and algae, and it's a big reason why plants are important for producing things economically. Since they use minerals as nutrients and gases like oxygen and carbon dioxide for respiration and photosynthesis, they've developed a wide range of enzymes, such as cytochrome P450s, to carry out many different chemical reactions. This helps explain the wide variety of plant secondary metabolites. P450s also play a role in making chemicals that help plants defend against harmful organisms, which are often found in animals as part of their detoxification processes. The different ways plants and animals have evolved together may also explain why plants have so many P450 types and why they're connected to human medicine.

Another thing that makes plants useful for synthetic biology is their variety of cellular compartments, such as the chloroplast, vacuole, nucleus, endoplasmic reticulum, and cytosol. Different biochemical steps can happen in specific parts of the cell, where there are special enzymes and conditions. Producing large amounts of these compounds is a big challenge in plant-based synthetic biology. This requires either expressing certain genes together or in a specific order. The different compartments in plants help by breaking down the whole process into separate parts, allowing each step to be optimized with the right conditions and starting materials. A method used in microbes for changing genomes has also been applied to plants through a technique called multiplex hybridization.

**Metabolic Engineering and Synthetic Biology (Sb) For Drug Production**

The production of natural product (NP) drugs, as discussed in previous sections, is often costly and results in low levels of the desired compounds.

However, the use of synthetic biology techniques can expand the range of pharmaceutical products that can be made efficiently. As our knowledge of biosynthetic pathways and their regulatory systems grows, we are seeing more successful applications of SB in metabolic

engineering for pharmaceuticals. Many pharmaceutical compounds are complex molecules with chirality, which are difficult to produce through chemical methods. Metabolic engineering combined with SB offers innovative solutions in red biotechnology by modifying organisms and introducing enzymatic pathways into industrial microbes. These microbes can convert natural feedstocks or process chemical precursors through enzymatic bioprocessing. Utilizing microbes as 'cellular factories' offers significant logistical advantages, including rapid growth cycles and the ability to utilize low-cost feedstocks. However, a persistent bottleneck remains: achieving industrial-level yields. While successes like semi-synthetic artemisinin demonstrate the power of modular gene tuning and metabolic flux optimization, many high-value compounds still fail to reach the 50 g/L threshold required for commercial viability. Future advancements will likely rely on automated, computer-aided design to better balance the redox and thermodynamic needs of these synthetic pathways. SB helps address this challenge by offering an engineering approach that combines modeling and simulation of metabolic pathways with the design, construction, testing, and optimization of host organisms.

Major classes of natural product drugs that are produced using biotechnology include isoprenoids, polyketides, non-ribosomal peptides (NPRs), and other naturally occurring polyphenols such as flavonoids and stilbenoids.

Isoprenoids are a large group of natural products (>40,000 unique compounds), including many pharmaceutical compounds like antioxidants, anticancer agents, and antimalarial drugs. The isoprenoid pathway has been expressed in various host organisms and assembled using genes from multiple sources. Several SB techniques have been employed to enhance the performance of these pathways, including modular tuning of gene expression, increasing flux, managing substrate toxicity, and using synthetic protein scaffolds for co-localization. A well-known example is the semi-synthetic production of artemisinin, an antimalarial drug, which was made possible through the integration of metabolic engineering and SB. The identification of limiting enzymes and gene expression balance using plasmid copy number and promoter strength led to the production of amorphadiene, a precursor to artemisinin, at 25 g/L in Escherichia coli and 40 g/L in yeast.

Similarly, SB techniques have been applied to the production of paclitaxel (taxol), a cancer chemotherapy drug. Taxol is challenging to make chemically, and its extraction from the Pacific yew tree is inefficient. Using a modular approach, the optimal expression levels for

parts of the taxol precursor pathway were determined, achieving a titer of 1 g/L in E. coli. A similar modular strategy was also used for the production of resveratrol, a nutraceutical, in E. coli.

SB can also be used to develop combinatorial biosynthesis of pharmaceutical compounds, such as non-ribosomal peptides like cyclic lipopeptide antibiotics, and to improve drug properties. For example, incorporating fluorine into the polyketide backbone of certain compounds leads to fluorinated natural products with enhanced absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties. SB has also been applied to combinatorial biosynthesis in plants. Plants have their own metabolic pathways, including cytochrome P450 enzymes, which are important for many biochemical reactions. In some cases, plants like tobacco, which have fast photosynthesis-driven biomass accumulation, can serve as an alternative bioreactor for pharmaceutical compounds. Cyanobacteria are natural producers of many natural products, including non-ribosomal peptides and polyketides. Blue-green algae (microalgae) and red algae (macroalgae) are also rich sources of diverse and novel bioactive compounds from marine environments. These organisms live in water and use sunlight for nutrients and energy, making them suitable for large-scale production of pharmaceuticals.

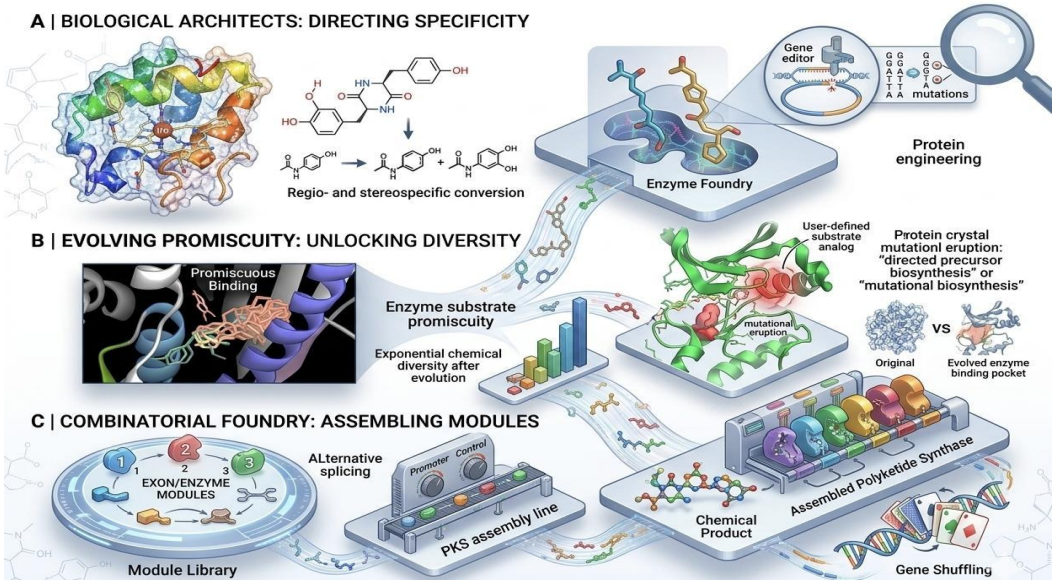


**Fig. 2: Synthetic Biology Innovation Platform for Chemical Diversity.**[21]

However, synthetic bioproduction is a complex process. Success depends not only on choosing the right pathway but also on many other factors such as cofactor and redox balance, thermodynamic feasibility, flux coupling, and regulatory elements. Synthetic

pathways are often inefficient and require improvement through protein engineering and directed evolution, which can be applied not only to individual enzymes but also to entire pathways. Automated computer-aided design can help manage the complexity of finding the most efficient pathway from many possible options. Based on this strategy, a fully automated framework using a retrosynthetic approach has been used for the production of flavonoid compounds. Flavonoids are promising pharmaceuticals because of their health benefits, with naringenin and pinocembrin serving as key scaffolds and precursors. Beyond these examples, integrating computer-aided design with automated DNA assembly, genome engineering, and robotized manufacturing could significantly speed up drug discovery and development in the future.

One of the most promising contributions of SB to pharmaceutical bioproduction is the use of biological devices made from well-characterized and standardized genetic parts to control pathway regulation and metabolic control. Metabolite-responsive transcription regulators and riboswitches are two types of genetic components that can be used to create synthetic, dynamically regulated metabolic pathways. For example, Zhang et al. developed a fatty acid synthesis pathway that is controlled by a transcription repressor that becomes inactive when it binds to fatty acids. This feedback loop increased the yield of fatty acid ethyl ester by three times and improved the stability of the pathway genes, enabling the high-yield production of other malonyl-CoA-derived compounds. Another area of SB for bioproduction is cell-free metabolic engineering, which involves the use of in vitro enzyme ensembles. Some research groups have been able to reconstruct biosynthetic pathways in the lab, for instance, for isoprenoids or for protein production.

## SYNTHETIC BIOLOGY STRATEGIES IN DD

### Target identification & validation

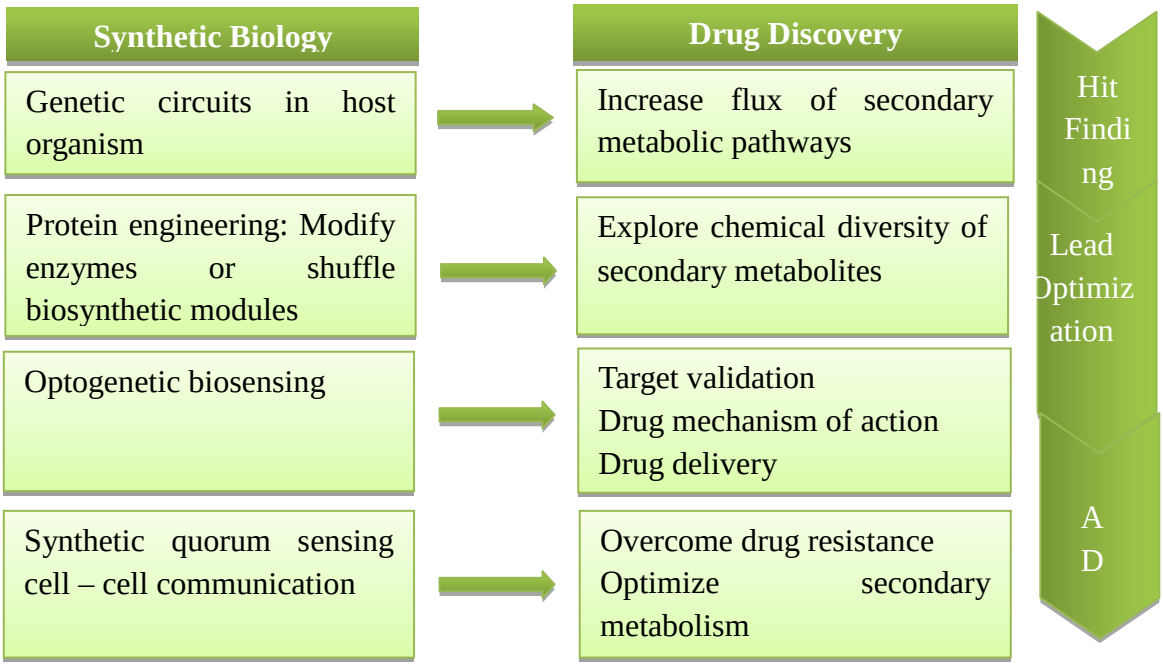


**Fig. 3: Synthetic biology tools in various steps of drug discovery.**[2]

The failure of drug discovery programs is mostly due to inadequate target identification and validation. Conversely, second-generation medications frequently capitalize on the success of first-generation drugs when targets are verified in the clinic through phenotypic or target-based approaches. Utilizing CRISPR-Cas9 techniques is a fantastic fit for this arena. This technique, which can finely alter genetic sequences, has made it possible to create a number of novel and crucial target validation components that have the potential to be extremely beneficial in the process of choosing the best targets. In essence, CRISPR-Cas9 has been effectively employed in pharmaceutical research for a number of years, supplanting outdated molecular biology techniques and offering the capacity to alter gene function by ablation, downregulation, upregulation, or mutation in a variety of cell types. CRISPR-Cas9 is set to make a big difference in target validation, thanks in part to concurrent advancements in intricately designed cell systems.

The use of primary cells in these settings is expanding, despite ongoing challenges with the types of cells available and the cost of these techniques. The ability to sustain and differentiate stem cells offers an opportunity to modulate and explore disease in a way that was not previously possible. For instance, recent studies have used primary T cells and stem cell-derived kidney cells to probe genes involved in illness, while Martufi et al. and

Borestrom et al. have used primary human fibroblasts and kidney cells to find factors involved in HIV infection and pathogenesis. Moreover, CRISPR-Cas9 provides genome-wide screening sets with the capacity to disrupt a gene's function, making them extremely potent instruments for quickly investigating the function of these genes in various cell models.

**Hit Generation**

Despite the fact that natural products have historically been a very effective source of pharmaceuticals, the modern drug discovery approach is now centered on the high throughput screening (HTS) of carefully selected compound libraries to find lead like molecules, which provide an easier source of equity for optimization. The current screening procedure includes the HTS of 1-2 million compound libraries, the screening of thousands of fragments using x-ray-guided optimization to find hit quality leads (micro molar activity), and the development of DNA-encoded libraries (DELs) recently to screen libraries of billions of compounds. The previously described artificially modified bioassays are essential to the hit finding procedure in these kinds of screens. Synthetic biology and data science, present new prospects for natural goods.

A more efficient method of identifying potential natural products for synthesis is to use bioinformatic searches of BGCs instead of screening natural extract libraries. DNA sequencing can now locate BGCs that are crucial for pharmaceutical effectiveness in natural product medications right beneath our feet. Many BGCs contain genes other than those involved in product production, such as transcription factors and potentially self-protective genes, in addition to the genes that code for enzymes. These self-defense genes produce detoxification enzymes, drug efflux transporters, and occasionally even resistant forms of the BGC-targeted protein. Numerous BGCs have multiple copies of these self-defense genes.

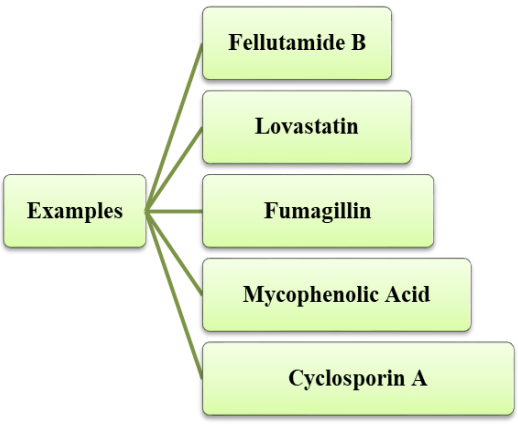


**Fig. 4: Examples of natural products with in-cluster resistance genes.**

## Lead Optimization

- **Directed Evolution & Synthetic Biology**

Lead optimization is the process of subjecting an initial lead compound to iterative rounds of (chemical) changes and characterisation in order to provide insight into its structure–activity relationship and metabolic stability. Hit identification and lead creation come first in this process. Directed evolution and lead optimization both share these iterative rounds of adjustments. A genetically encoded molecule (nucleic acids, proteins, or peptides) is modified or mutated repeatedly in directed evolution, with the end goal being the selection or screening of a user-defined candidate while guaranteeing the inheritance of the evolved molecule's advantageous trait (genotype–phenotype linkage). For instance, directed evolution has led to the emergence of cyclic peptides that block HIV protease and linear peptides that target G-protein subunit α. The development of methods such as PACE,52 in vivo continuous evolution (ICE), CRISPR-AID, orthogonal replication (OrthoRep), and EvolvR that enable continuous directed evolution in a range of host organisms has accelerated recently. NRPs and RiPPs, two groups of the previously mentioned peptides, are prospective lead molecules for therapeutic research.

- **Late-Stage C–H Functionalization of Drug Leads Using Engineered Enzymes**

Bioactive compounds can be structurally altered in the early stages of drug discovery by replacing one or more specific atoms, adding others, or deleting others. When creating libraries of pharmacological lead analogs, this method—also known as molecular editing or late-stage functionalization, or LSF—is typically quicker and less expensive than de novo synthesis. As demonstrated by the significant impact of a halogen-bonding interaction or the addition of a single methyl group, which significantly increases kinase inhibitor selectivity, even a small structural alteration can have a profound effect on a drug's characteristics. The identification of drug lead derivatives with optimal activity, safety, and/or drug metabolism/pharmacokinetic (DMPK) profile could therefore be sped up significantly with the help of LSF.

New techniques in photoredox, metallophotoredox, transition metal, and other chemical domains have shown to be effective tools for LSF in drug discovery labs over the past 20 years. Synthetic biology has seen tremendous progress in the past few years, and these developments could potentially bridge the gap left by synthetic chemical techniques.

Synthetic biology uses technologies from various fields, such as molecular biology, protein engineering, metabolic engineering, and bioinformatics, to develop non-natural biological systems for novel purposes. Enzyme directed evolution has made a significant contribution to the advancement of synthetic biology. The 2018 Nobel Prize in Chemistry given to Prof. Frances Arnold for her exceptional contributions to directed evolution serves as evidence of the applicability of this technology.

Apart from the directed evolution of enzymes, the application of rational and semi rational design has also shown to be highly effective when mechanistic data, x-ray crystal structure data, or high-quality homology models are available. Using well-established techniques, such as epPCR, DNA shuffling, single-site saturation mutagenesis, and combinatorial active-site saturation test (CAST), the creation of large mutagenesis libraries may now be accomplished quickly and affordably.

Notably, in the area of enzyme engineering, machine learning is drawing more and more interest for prediction and decision-making. Because of all these initiatives, there is currently a great deal of potential for tailored robust and selective enzymes to accelerate various pharmaceutical sector projects, including drug discovery.

## APPLICATIONS

- **Metabolic Engineering**

The range of pharmaceutical items that can be effectively generated can be increased by using SB techniques. More successful applications of SB for pharmacological metabolic engineering are emerging as our knowledge of the intricate regulatory networks underlying biosynthetic pathways grows. Pharmaceutical chemicals are frequently chiral compounds that are challenging to synthesize chemically. By altering and introducing enzymatic pathways into industrial organisms for the conversion of natural feedstock and/or enzymatic bioprocessing of supplied chemical precursors, metabolic engineering, when paired with SB, offers creative possibilities for red biotechnology. Since it can be better controlled, has a faster growth rate, and can often be produced with affordable substrates, microbial bioproduction is often preferred.

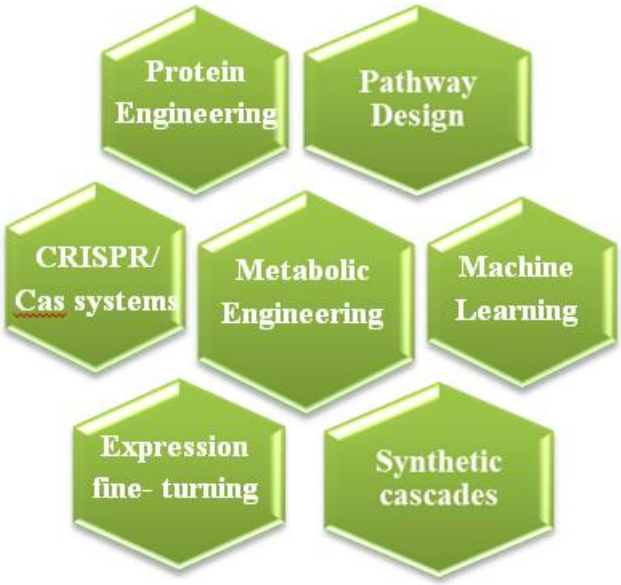


**Fig. 5: Technologies commonly used in synthetic biology.[3]**

Even though it is a promising method for producing pharmaceuticals, only a limited number of compounds with pharmaceutical interest have reached the industrial bioproduction scale (50 g/L), including some amino acids and isoprenoids. In contrast, several antibiotics and artemisinin have reached the medium bioproduction scale (5–50 g/L). Increasing the number of pharmaceuticals that can be bioproduced at industrial scale is, thus, a challenge at present. One of the current challenges is to increase the number of medications that can be bioproduced at an industrial scale. Recent years have seen advancements in the heterologous synthesis of significant natural compounds, including alkaloids, polyketides, terpenoids, and non-ribosomal peptides.

- **Synthetic biology in drug delivery**

Typically, the synthetic biology structures are housed in carriers to enable their in vivo functionalities. Viral vectors' applications for modifying the human genome are limited by safety issues. As a result, non-viral carriers are coming under increasing scrutiny. Utilizing genome engineering tools and genetic circuits, among other medicinal agents, nanotechnology can help deliver. More options for targeted and controlled release in DNA/RNA delivery systems are now accessible thanks to advancements in nanotechnology. One such example is the liposome-based DNA/RNA delivery system, which has been shown to be a viable and efficient gene therapy technique. A range of synthetic lipid vectors have been approved for use in clinical settings.

- **Cell-free synthetic biology in medical applications**

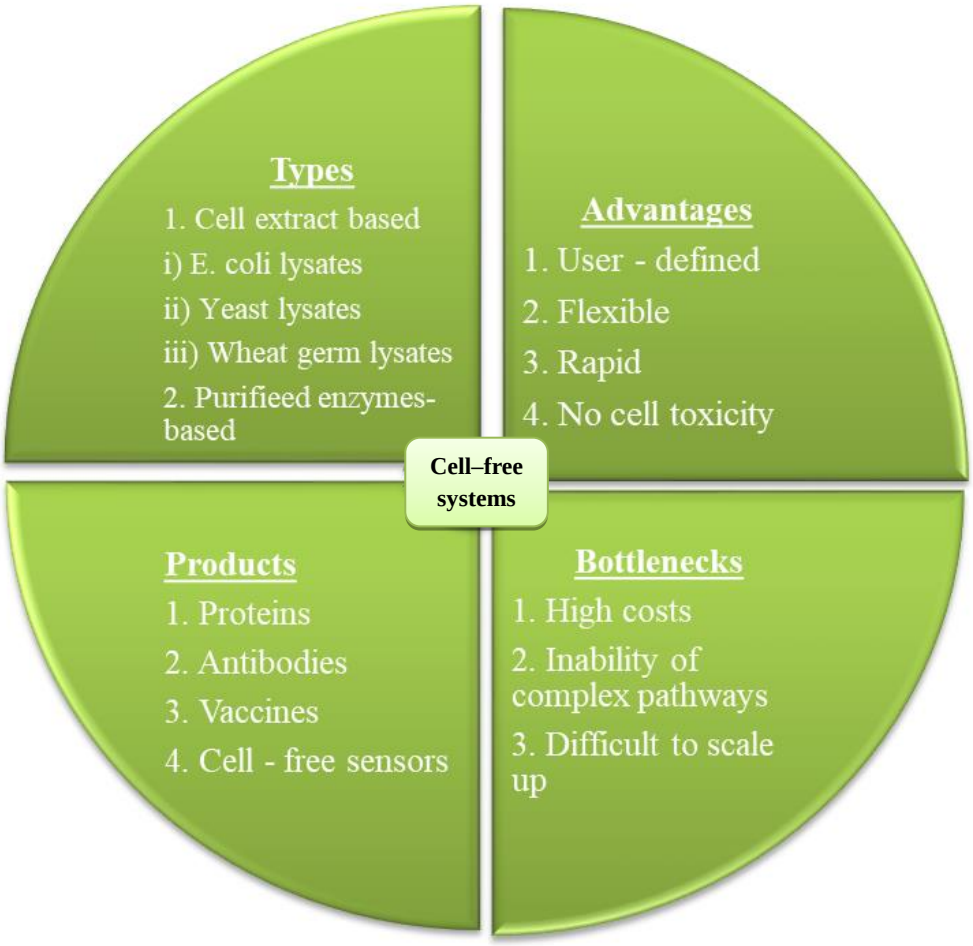


**Fig. 6: The types, advantages, products, and bottlenecks of cell-free systems.**[3]

Up to now, the main goals of synthetic biology have been to build genetic circuits, biological modules, and reprogramme organisms. Nevertheless, the complexity of living things has impeded advancements in synthetic biology due to our inadequate understanding of how life functions. Systems that are user-defined can address the issue. A system that does not require living cells to conduct biological tasks in vitro, such as transcription and translation, is known as a cell-free system.

A high tolerance to cytotoxicity, ease of control, flexibility, and openness have made the system useful for synthesizing proteins that are toxic or hard to produce in cells. Moreover, high-throughput screening works well with cell-free systems. The disciplines of medicine and pharmacy have recently benefited from the applications of cell-free synthetic biology, thanks to developments in lyophilization and cell-free bio sensing diagnosis.

## CONCLUSION AND FUTURE PERSPECTIVES

Synthetic biology has significantly expanded and achieved several successes in both science and application aspects since the field's rapid advancements began more than ten years ago. The next generation of therapeutic approaches is going to be individualized designed medicine. Smart medicines that rely on circuits encoded with genetic information to translate environmental cues into actions of effectors will be widely employed. The auto-regulated therapeutic cells are one-stop solutions for illness prevention, diagnosis, and therapy. They recognize diagnostic inputs for therapeutic outputs. While some applications, such as CAR-T treatments, are already in clinical trials, the majority of smart cells are not. Numerous early clinical initiatives have been unsuccessful, primarily due to limited therapeutical efficacy and unanticipated side effects in humans. Future research should focus on treatment stability and efficacy in addition to patient safety.

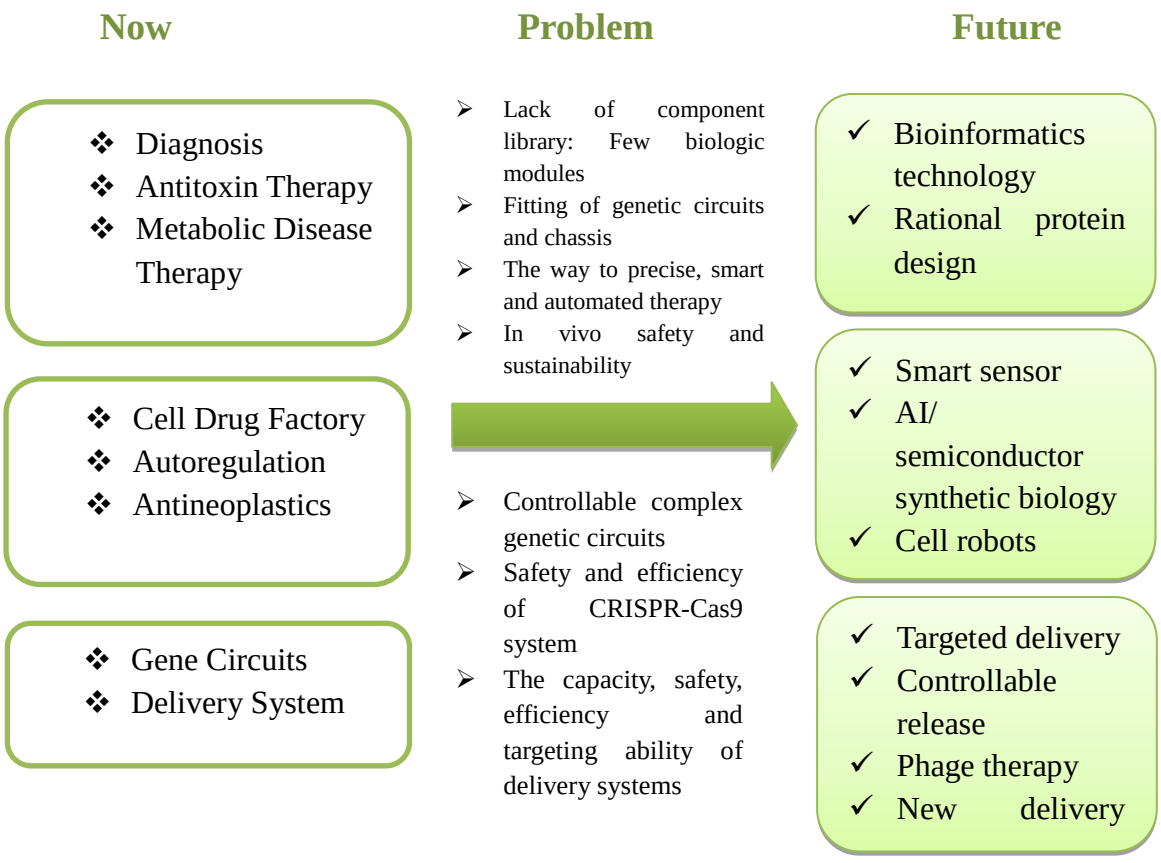


**Fig. 7: The present situations, technical bottlenecks and future developments of synthetic biology based gene therapies.**[3]

To further push the boundaries of drug development, workflows combining synthetic biology and chemistry with contemporary technologies like artificial intelligence and machine

learning are starting to emerge. All phases of drug discovery and development are undoubtedly impacted by synthetic biology, and potential to have an even greater impact on the drug research and development value chain may arise from the discipline's contribution being recognized.

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