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Synthetic Biology in Drug Discovery as a Source of Discovery in Translation Biomedicine

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Abstract

The declining cost of DNA synthesis, improvements in genetic engineering, expanding knowledge of genome organisation, and boom in data science, the influence of synthetic biology on the world has been escalating [1]. But a lot of the discipline's use in the pharmaceutical sector is still unclear. The influence of synthetic biology on target validation, assay development, hit discovery, lead optimization, chemical synthesis, and the creation of cellular therapies is highlighted in this review's current examples. We also emphasise the accessibility of the technology and resources powering the field [2]. All phases of drug discovery and development are undoubtedly impacted by synthetic biology, and the prospects for the drug discovery and development value chain may grow as a result of the discipline's contribution being acknowledged [3].

Keywords: Biofoundry, Chassis Organism, Crispr-Cas9, Drug Discovery, Late-Stage Functionalization, Synthetic Biology

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Introduction

Synthetic biology is the creation and fabrication of new biological entities like enzymes, circuits, modules, or systems, as well as the redesign of current biological systems by the reprogramming of genetic information for advantageous uses. It has been evolving since the 1960s1, but has grown significantly over the past ten years, in part due to the declining cost of DNA synthesis, development engineering, and improvements in our understanding of how the genome is organised as well as data science. However, a large portion of what surrounds this mysterious and fascinating topic has been a part of molecular biology for as long as we can recall [4]. The emphasis on the design and creation of essential components that can be modelled, comprehended, and tuned to achieve specific goals sets synthetic biology apart from conventional molecular and cellular biology [5]. These smaller components and devices are assembled into bigger integrated systems to tackle certain issues after being analysed, understood, and optimised to satisfy specified performance standards [6]. What distinguishes synthetic biology from other forms of biology, and why is now the perfect time for this discipline to hold such promise for the pharmaceutical industry? We want to highlight some of the most practical and exciting applications of synthetic biology in medication development in this study [7]. We outline the effects this developing field has already had on the pharmaceutical sector and discuss how it may further improve the value chain for drug discovery [8]. The three main factors that govern the productivity of the pharmaceutical sector are speed, cost, and quality [9]. Concentrating on enhancing the effectiveness of drug discovery All three are essential components that have been improved because to the use of synthetic biology technologies [10]. However, significantly alternative methods from the traditional laboratory-based design-make-test cycles that serve as the foundation for iterative compound design are needed for the game-changing acceleration of drug discovery [11]. While the pharmaceutical industry has considerable support for the use of artificial intelligence and automated chemistry3,4, the potential use of synthetic biology beyond tool-based advancements is comparatively underappreciated and without particular acknowledgement. Its significance has been undervalued outside of the pharmaceutical business as well [12]. According to a recent Economist article, the revenue generated by genetically modified organisms supported numerous reviews and scientific articles discuss how synthetic biology may influence drug discovery and lead to the development of novel treatments [13]. However, they have only been able to clearly characterise a handful instances where synthetic biology has already altered medication development [14]. The guided evolution of therapeutic monoclonal antibodies has altered the face of contemporary drug therapy, although many pharmaceutical specialists, in the authors' opinion, would be unable to pinpoint

a single synthetic biology effect on innovative medications [15]. Contrary to the low attention within the pharmaceutical sector, one of the most innovative medical techniques, employing chimeric antigen receptor T cells, was created by combining possibly the two most interesting areas of synthetic biology, cell therapy and genetic reprogramming. We align some of the fascinating synthetic biology approaches to drug development in this review. Starting from the synthetic biology toolbox and the design-make-test-learn cycle, analogous to the design-make-testanalyze cycle of medicinal chemistry. We also highlight the most inventive and revolutionary works in each section, which, albeit a personal choice, can at least serve as recent years have seen significant advancements in the design of biological circuits, the creation of strong synthetic biology chassis organisms, and high-throughput screening methods that are starting to speed up the process of contemporary drug discovery. Synthetic biology has advanced significantly as a result of significant decreases in the cost of DNA synthesis and sequencing, such as the ability to create DNA-encoded drug libraries and the discovery of novel biosynthetic gene clusters by genome mining. Escherichia coli and Saccharomyces cerevisiae are important synthetic biology chassis species in this. For quick creation and characterization of genetic devices and systems as well as for the convenience of part interchange, modular design concepts are crucial.

Discussion

Additionally, an orthogonal mode of action is required to distinguish biosynthetic activities from the chassis cell's intrinsic regulatory networks, whose activity is unpredictable and may produce background noise as a result of external stimuli or cell cycle progression. Synthetic biology applications are based on the idea of design-build-test-learn cycles. From proof-of-concept investigations sophisticated drug discovery screens and genetic circuit design in living therapies, it enables effective screening and optimization for desired activities of biosynthetic devices and systems of interest. The design phase makes use of both computer-assisted methods and well-characterized biological components. These components include ways to precisely control tags for protein degradation. 19 Synthetic promoters are being created at an increasing rate, enabling for strong fine-tuning of gene expression and orthogonal function. The use of a central promoter region with binding sites for heterologous/hybrid transcription factors21 or Cas9 linked to transcriptional regulators are examples of strategies. 22, 23 a direct control input to the system frequently requires inducible modulation of expression by external stimuli. 24,25 Activators, repressors, reporters, and environment- or drug-responsive biosensors are examples of genetic devices whose behaviour is adjusted and characterised using the aforementioned approaches. To speed up this design phase and enable laboratory automation and open data reporting, computational tools like AutoBioCAD, Cello, and the Synthetic Biology Open Language (SBOL) 27 were created. During the development stage, effective DNA assembly tools, such as Various in silico modelling techniques are used for simulation and optimization in the learn stage. This involves the use of differential equations and machine learning methods, as was recently demonstrated for the model-guided creation of artificial yeast promoters or the rational tuning of G-protein-coupled receptor signaling39. For instance, recently used to improve the dynamic and operational range of a metabolite-responsive biosensor, design of experiment tools examine the multidimensional experimental space allowing for modelling and optimization. The rising use of automation and software development, which integrates the many DBTL cycle components in an industrial-like pipeline and makes it possible to characterise thousands of parts and biosynthetic designs, is one of the cycle's primary future drivers. A Global Biofoundry Alliance44 was recently established to coordinate efforts in the sector globally. The idea was given the name "biofoundry." Direct cell treatments are being created using synthetic biology-engineered *E. coli*, as will be discussed in the Cell Therapy and Biologics section.

Conclusion

The first therapeutic bacteria have already entered phase I and phase II clinical trials for a variety of diseases, including hyperammonemia phenylketonuria 58, 59, and oral mucositis, in addition to other instances in the preclinical stage. 60 Although these novel therapies show tremendous potential for a wide range of future uses, safety, regulatory, and public issues need to be resolved before they can be made commercially available. Despite being widely employed in research and having a successful track record for drug screening methods, *E. coli* has several restrictions when it comes to Additionally, considering its potential for producing drugs for sale, E. The drawback of coli-based bioprocesses is that they are vulnerable to phage infection. They are more expensive to purify because their endotoxin membrane structures are pyrogenic. Unlike bacterial hosts like *E. coli, coli*, *S. Cerevisiae* possesses extensive membrane structures like the endoplasmic reticulum and Golgi apparatus as well as intracellular organelle systems. Recent impressive examples demonstrating the power of yeast as a synthetic biology chassis are the production of various plant-derived complex natural products 80,81. These products include cytochrome P450 monooxygenases, which are essential for the biosynthesis of many natural products with high structural diversity. Contain strictosidine; a precursor of the powerful chemotherapeutic alkaloid monoterpene indole, In addition to the traditional synthetic biology chassis outlined above, various non-traditional chassis species may be more advantageous for the synthesis of certain chemical groups. 87 This includes, for example, Streptomyces, which is used for its capacity to produce large amounts of natural products such as polyketides, no ribosomal peptides, and terpenes, as well as Bacillus subtilis, which is used for its high secretion capacities for the production of enzymes and some nutraceuticals. Lactic acid bacteria are also used for their use as living therapeutics. 9 The appropriate chassis organism will rely on a number of factors, such as its intended use, the target chemical class, the significance and accessibility of synthetic biology methods, screening libraries, or even considerations toward that goal.

Acknowledgement

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Conflict of Interest

None

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