IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Synthetic Biology applications for Antibiotic Resistance

Sanglipong Lemtur

Research Scholar

Jawaharlal Nehru University

Antibiotic resistance is a problem that modern medicine is struggling to solve. Its entanglement with society and economics means that it is not just a medical issue, but one with far-reaching implications for public health. Furthermore, with the drying up of new discoveries of new antibiotics, a renewed interest in non-antibiotic-based approaches to treating bacterial infections is needed if we are to continue to fight against drug resistance. This article explores some ways in which synthetic biology can be applied to overcome antibiotic resistance.

1. Introduction

According to the Biotechnology Innovation Organisation (BIO), "Synthetic biology is a new interdisciplinary area that involves the application of engineering principles to biology. It aims at the (re)-design and fabrication of biological components and systems that do not already exist in the natural world" (Biotechnology Innovation Organisation, 2016. p. n.a). In simple terms, synthetic biology uses the knowledge of genetics in order to make artificial biological systems which already naturally exists and some which have been synthetically designed. These biological systems are then given a function which is otherwise not seen in nature, or which have not been discovered in nature already. To put it more succinctly, it is a discipline which endeavours to develop new processes and incorporate them into organisms in order to address specific problems. Hence, it is considered to adhere to a bottom-up approach of building systems (Cole, 2014). However, this is only one facet of the discipline. Nevertheless, what is most unique to the foundation of this discipline was the novel idea that engineering principles could be used to study as well as facilitate the manipulation of cellular systems for our benefit.

However, the quality of the field of synthetic biology makes it difficult to define what it encompasses (Nature Biotechnology, December 2009), with definitions that often overlap into other already established fields. In this light, it is important to state that synthetic biology professes to be an interdisciplinary approach (Müller & Arndt, 2012, p. 24). One striking difference with its sister discipline, biotechnology, is that while the former involves the transfer of single genes from one cell to another, synthetic biology envisages the assembly of whole

genomes from a set of 'standardized genetic parts' that are then inserted into a recipient microbe or cell. In a sense, synthetic biology aims to engineer biological systems, modifying them genetically to perform functions that do not exist in nature. The novelty in the technique revolves around that aspect of the discipline which involves the use of reusable, standard interchangeable biological parts (Saeidi, et al., 2011). Hence, standardisation finds itself as a fundamental principle in synthetic biology which is a feature incorporated from modern day engineering (Zhao & Medema, 2016, p. 920). In the same sense as is understood in engineering, by enabling modularity and interchangeability of parts, standards are incorporated into biological devices (*ibid.*). This feature elevates synthetic biology "from merely tinkering with natural biological systems to conceptual design-based engineering of novel biological devices from standardized parts" (*ibid*. p.920).

Although there are areas of public health which cannot simply be addressed by technology, one aspect of the argument to be made here is it that the technology might assist us to tackle diseases for which we do not have any cure or solutions currently. Antibiotic resistance for instance is one such problem in need for solutions, furthermore, synthetic drugs have been manufactured for a long time now, starting with insulin in 1978[1]. However, the perils of relying wholly on technology and not sufficiently on other more basic mediations for food, housing, clothing, and basic healthcare still perseveres.

1.1 Synthetic biology for public-health

Nevertheless, it has been stated very often, about synthetic biology, that we are only limited by the stretch of our imagination as to what we can do with this new technology. The first benefit of synthetic biology, Chen & Lu envisage, is in metabolic engineering. That is, through optimizing the biosynthetic pathways to maximize yields of desired output (Cheng & Lu, 2012, p. 166). These desired products may vary from artemisinin production to non-natural amino acids. Additionally, in bio-medicine, they believe that it has the potential to engineer novel 'diagnostic and therapeutic strategies for relatively intractable medical conditions such as cancer and infectious diseases' (*ibid*. p. 166). Hence, some of the most beneficial outcomes from synthetic biology to public health could be in the diagnosis of a health conditions through designing diagnostic tools and the other in the creation of new medicines for stubborn diseases. Therefore, synthetic biology promises to be an innovative field in medicine, and further advances in its parts and circuit design will not only allow progress to the development of programmable cells but also the application of targeted applications (Cheng & Lu, 2012, p. 166).

As such the application of synthetic biology in public health professes to have the ability to help improve the health of the people drastically. Also, with the cost of synthesizing DNA becoming cheaper we could see further advances leading to better health conditions. This reads very analogous to what biotechnology promised, and just like in biotechnology the main question, other than on biosafety and security, should concentrate on whether

[1] Synthetic insulin was first made in 1978 by scientists at Genetech, Inc. and City of Hope National Medical Centre. Scientists used recombinant DNA gene technology to synthesize human insulin. Where previously, producing insulin from pig and cattle pancreas glands were the only viable method, the use of animals to produce insulin did cause some allergic reactions, as it was not a true human match to insulin.

the investments in synthetic biology would only remain speculative? There is also the question of ethics and also the appropriateness of the technology.

But so far, this technology has been used to construct novel biological systems to produce drugs (Ro et al, 2006) and biofuels (Steen, et al., 2010), to degrade containments in water (Sinha et al, 2010)[2], and to kill cancer cells (Anderson, Clarke, Arkin, & Voigt, 2006). Other novel bio-organisms could perform cell-based synthesis of useful materials- to clean up oil spills (Biello, 2015), detect food spoilage, and clean drinking water pools, to name a few. Therefore, such technologies could assess and remediate natural and human made ecological conditions which are connected to the wellbeing of the immediate population (bioremediation). More significantly, for the problem under consideration in this article, synthetic biology has made effective advances in the sensing and killing of bacteria (Saeidi, et al., 2011). Hence, making new antimicrobials through synthetic biology could overcome the innovation gap that currently exists, considering the last major scaffolds for antibiotics were discovered almost half a century earlier (Fischbach & Walsh, 2009).

1.2. Synthetic biology for the design of new antimicrobials

So how do you design a microbial chassis which can kill the bacteria? Researchers have showed success in taking advantage of the natural processes of the *Pseudomonas Aeruginosa* to create a precise bio-phagic intervention against it. The fact is that, the *Pseudomonas Aeruginosa* competes with its own species by producing toxic proteins called *pyocins*, and a team from Singapore exploited this molecular system by incorporating *E. coli* with the *pyocinS5* gene (Saeidi, et al., 2011). *P. aeruginosa* generally causes urinary tract infections, gastrointestinal infections, and other systemic infections in people. It an opportunistic pathogen that is a leading cause of morbidity and mortality immunocompromised individual, and have been found to be resistant to conventional antibiotics *a variety of antibiotics, including aminoglycosides, quinolones and β-lactams* (Pang et al., 2019). The character of its preciseness is gained due to the fact that each pyocin targets only certain bacterial strains, the toxin will not kill other bacteria living in the body. This is because pyocins are the *Pseudomonas* bacterium's own species-specific antibiotics[3]. Such innovations, other than providing new remedies, could also solve the problem of microbiome disruptions caused by broad spectrum antibiotics.

Furthermore, considering the fact that diagnosis is a major issue in the treatment of infectious diseases, like tuberculosis, we can perceive many benefits. The added complexity due to the development of multi-drug resistant and extensively drug resistant bacteria also require consideration for the quick adoption of new methods and technologies. In this aspect, synthetic biology could provide a feasible solution as a recourse to drug discovery and development of alternative strategies to combat such problems (Saxena, Mukherjee, Kumari, Singh, & Lal, 2014) (Abil, Xiong, & Zhao, 2015). In 2002, one of the earliest opportunities to fast track traditional approaches to developing antibiotics was recognized when researchers at the Wellcome Trust Sanger

[2] This paper was retracted due to the authors' inability to reproduce their result on two separate occasions. However, this should not be taken to mean that such procedures are not possible but just demonstrates the difficulty of the process of synthesizing new organisms. The authors' paper: *'Reprogramming bacteria to seek and destroy an herbicide'* (Nat. Chem. Biol.6, 464–470 (2010); published online 9 May 2010; retracted 14 February 2014).

[3] The authors (Saeidi, et al., 2011) believe that using pyocins instead of broad-spectrum synthetic antibiotics might help slow the spread of antibiotic resistance. http://www.nature.com/news/2011/110816/full/news.2011.483.html (last accessed) on 17/04/16

Institute in Cambridge, UK, published the genome sequence of the antibiotic-producing bacteria Streptomyces coelicolor (Bentley et al., 2002). This work revealed many other genes within the *S. coelicolor* that could potentially be capable of synthesising other antibacterial natural products(Wright, 2014). Furthermore, organisms are naturally capable of producing metabolites with antimicrobial characteristics but at very low capacities, however with the unravelling of biosynthetic mechanisms and the tools of synthetic biology it is possible to increase and modify such functions(Zhang et al., 2020).

Hence, the tailoring of new enzymes and the ability to expand the chemical diversity natural products could usher in a new hallmark in the production of antibiotics (Enam, 2021). Glycopeptide antibiotics (GPAs) provide a useful illustration of how attempts have been made to investigate the application of synthetic biology methods in an effort to increase the chemical diversity of a class of natural products (Thaker & Wright, 2015), especially with low toxicity and high specificity. The difficulty arises in the unpredictability of the response of such synthetic compounds in different hosts, in establishing the safety of such a technology, and also in turning around public opinion.

Conclusion

The global market dynamics show that there are strong drivers for this synthetic biology technology, and its relevance to field of medicine is truly boundless, including its implication for public health. But while the investments in research, advances in technology and government support for institutions provide encouragement to this industry; by helping drive down cost and allowing by encouraging novel inventions, the absence of a regulatory framework heightens concerns pertaining to biosafety and biosecurity.

It would be pertinent to ask whether this new venture in science may lead to the already increased techno-centric way of looking at health. Clubbed with this is the inherent weakness of the industry which is its heavy reliance on biomass (to provide the substrate used as a growing medium). This aspect of the industry has been criticized by environmentalist for its heavy dependence on water and how the sugar industry takes away from land that could be used for the production of food.

The technology has within it the potential to enhance the quality of life of people not through purely medical mediation, but by influencing other aspects of life that have a direct correlation to health. However, this field lacks in studies based on the risks of this technology, but as we observed from the trends in research relating to synthetic biology it may be not long before questions relating to risk and ethics also are researched upon. Hence, as a concluding thought, given its' still early stage we must not be hasty in arguing along the 'half-pipe of doom' but consider encouraging further explorations into its potentials and perils. One potential area where we may already be seeing a place for this relatively novel technology is in health genomics.

Bibliography

Abil, Z., Xiong, X., & Zhao, H. (2015). Synthetic Biology for Therapeutic Applications. *Molecular Pharmaceutics*, *12*(2), 322. https://doi.org/10.1021/MP500392Q

Bentley, S. D., Chater, K. F., Cerdeño-Tárraga, A. M., Challis, G. L., Thomson, N. R., James, K. D., Harris, D. E., Quail, M. A., Kieser, H., Harper, D., Bateman, A., Brown, S., Chandra, G., Chen, C. W., Collins, M., Cronin, A., Fraser, A., Goble, A., Hidalgo, J., … Hopwood, D. A. (2002). Complete genome sequence of the model actinomycete Streptomyces coelicolor A3(2). *Nature 2002 417:6885*, *417*(6885), 141–147. https://doi.org/10.1038/417141a

Cheng, A., & Lu, T. K. (2012, April 7). Synthetic Biology: An Emerging Engineering Discipline. *The Annual Review of Biomedical Engineering 16:14*, 155 - 178.

Chubukov, V., Mukhopadhyay, A., Petzold, C. J., Keasling, J. D., & Martín, H. G. (2016, April). Synthetic and systems biology for microbial production of commodity chemicals. *npj Systems Biology and Applications 2, no. 16009*, 1-11. doi:doi:10.1038/npjsba.2016.9

Cole, J. (2014, December). Editorial introduction for the Synthetic Biology thematic issue. *New Biotechnology, 31*(6), 525 - 527.

Enam, F. (2021). Harnessing synthetic biology to expand chemical diversity of antibiotics. *Synthetic Biology*, *6*(1). https://doi.org/10.1093/SYNBIO/YSAA029

Fischbach, M. A., & Walsh, C. T. (2009). Antibiotics for emerging pathogens. *Science (New York, N.Y.)*, *325*(5944), 1089–1093. https://doi.org/10.1126/SCIENCE.1176667

Guzmán-Trampe, S., Ceapa, C. D., Manzo-Ruiz, M., & Sánchez, S. (2017). Synthetic biology era: Improving antibiotic's world. *Biochemical Pharmacology*, *134*, 99–113. https://doi.org/10.1016/J.BCP.2017.01.015

How Microbes Helped Clean BP's Oil Spill - Scientific American. (n.d.). Retrieved December 29, 2022, from https://www.scientificamerican.com/article/how-microbes-helped-clean-bp-s-oil-spill/

Müller, K. M., & Arndt, K. M. (2012). Chapter 2: Standardization in Synthetic Biology. In W. Weber, & M. Fussenegger (Eds.), Synthetic Gene Networks: Methods and Protocols, Methods in Molecular Biology (Vol. 813, pp. 23-43). Springer. doi:DOI 10.1007/978-1-61779-412-4_2

Pang, Z., Raudonis, R., Glick, B. R., Lin, T. J., & Cheng, Z. (2019). Antibiotic resistance in Pseudomonas aeruginosa: mechanisms and alternative therapeutic strategies. *Biotechnology Advances*, *37*(1), 177–192. https://doi.org/10.1016/J.BIOTECHADV.2018.11.013

Saeidi, N., Wong, C. K., Lo, T.-M., Nguyen, H. X., Ling, H., Leong, S. S., . . . Chang, M. W. (2011). Engineering microbes to sense and eradicate Pseudomonas aeruginosa, a human pathogen. Molecular Systems Biology 7; Article number 52.

Saxena, A., Mukherjee, U., Kumari, R., Singh, P., & Lal, R. (2014). Synthetic Biology in Action: Developing a Drug Against MDR-TB. *Indian Journal of Microbiology*, *54*(4), 369. https://doi.org/10.1007/S12088-014-0498-0

Sinha, J., Reyes, S. J., & Gallivan, J. P. (2010). Reprogramming bacteria to seek and destroy an herbicide. *Nature Chemical Biology*, *6*(6), 464–470. https://doi.org/10.1038/NCHEMBIO.369

Thaker, M. N., & Wright, G. D. (2015). Opportunities for Synthetic Biology in Antibiotics: Expanding Glycopeptide Chemical Diversity. *ACS Synthetic Biology*, *4*(3), 195. https://doi.org/10.1021/SB300092N

Wright, G. (2014). Perspective: Synthetic biology revives antibiotics. *Nature 2014 509:7498*, *509*(7498), S13–S13. https://doi.org/10.1038/509s13a

Zhang, F., Gao, D., Lin, J., Zhu, M., Zhuang, Z., Duan, Y., & Zhu, X. (2020). Construction of Inducible Genetic Switch for the Global Regulator WblA To Sustain Both Overproduction of Tiancimycins and On-Demand Sporulation in Streptomyces sp. CB03234. *ACS Synthetic Biology*, *9*(6), 1460–1467. https://doi.org/10.1021/ACSSYNBIO.0C00114

Zhao, H., & Medema, M. H. (2016, March). Standardization for natural product synthetic biology. Natural Product Reports(33), 920-924. doi:10.1039/c6np00030d

Click or tap here to enter text.