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Synthetic biology: Application in disease diagnosis

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Abstract
Synthetic biology is a logical extension of what has been called recombinant DNA (rDNA) technology or genetic engineering since 1970s. The subject combines various disciplines from within these domains, such as biotechnology, evolutionary biology, molecular biology, systems biology, biophysics, computer engineering, and genetic engineering. Synthetic biology aims to understand whole biological systems working as a unit, rather than investigating their individual components and design new genome. It has the potential to take the industry to new heights in coming years. Synthetic biology advances have been driven by dramatic cost reductions in DNA sequencing and DNA synthesis; by the development of sophisticated tools for genome editing, such as CRISPR/Cas9; and by advances in informatics, computational tools and infrastructure to facilitate and scale analysis and design.
It is a relatively new field with the key aim of designing and constructing biological systems with novel functionalities. Today, synthetic biology devices are making their first steps in contributing new solutions to a number of biomedical challenges, such as emerging antimicrobial resistance and cancer therapy. Recent approaches and applications of synthetic biology include disease mechanism investigation and disease modeling, drug discovery and production, vaccine development and treatment of infectious diseases, cancer, and metabolic disorders. Similarly, progress is being made with 'synthetic approaches' in genetics and animal sciences, providing exciting opportunities to modulate, genome design and finally synthesis of animals for favorites traits.
Synthetic biology will potentially transform our response in combating future pandemics. Unleashing the full power of synthetic biology with appropriate regulations and checks will gear our society towards a healthier and safer future.

Keywords: Synthetic biology, application, diagnosis

Introduction
It is a multidisciplinary field of study that aims to create new biological components, tools, and systems or to remodel existing natural systems. It incorporates concepts from engineering, biology, biotechnology, bioinformatics, mathematics, and chemistry.

Synthetic biology comes in two broad classes
Unnatural molecular biology
To replicate emergent phenomena from natural biology using artificial molecules in an effort to build artificial life.

Bioengineering & protocell synthetic biology
Using interchangeable biological components to create systems that don't naturally work.

History (Source: PubMed with the keyword 'Synthetic Biology')

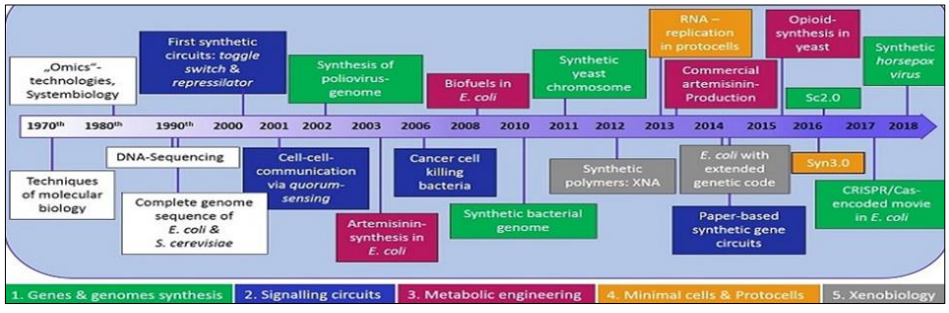


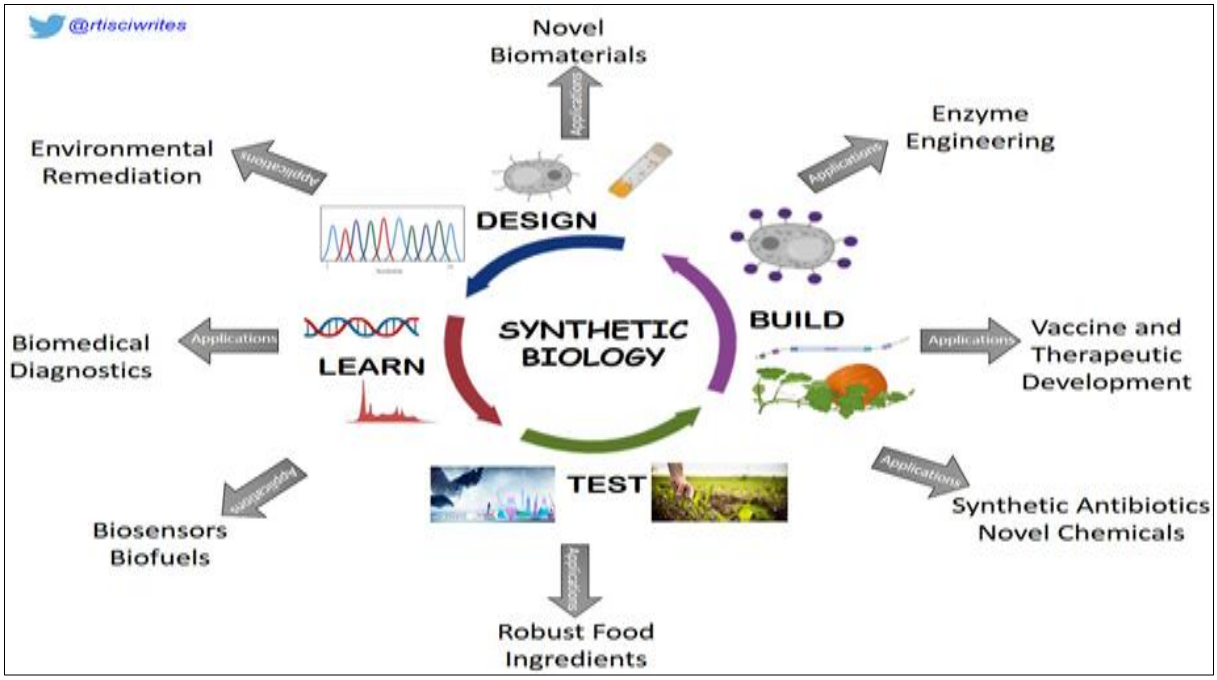
Fig 1: History of Synthetic Biology

The ability to create new living entities with tailored functions from simple laboratory chemicals is now possible thanks to the construction of a whole DNA sequence from scratch.

Applications of synthetic biology

Synthetic Biology can apply in following area:

1. Medicine and pharmaceuticals
2. Biofuels and sustainable energies
3. Environmental bioremediation
4. Food and agriculture
5. Space system and exploration



https://www.molecularcloud.org/p/using-synthetic-biology-to-combat-pandemics-what-why-how

Fig 2: Applications of Synthetic biology

Scopes of synthetic biology in disease diagnosis

To contribute to finding solutions for biomedical problems like the escalating spread of new infectious illnesses and the evolution of cancer medication resistance. Synthetic biology anticipates the creation of specially crafted, easily controlled, and secure devices that would support human immune systems and correct metabolic anomalies to solve these issues. The topic focuses on current developments in synthetic biology that show promise for the creation of human therapies in the future. 1) The various synthetic biology techniques that have recently been applied to modelling and research into disease mechanisms. 2) Some recent instances of the field's contributions to the development of new drugs. 3) Finally, examine current developments in synthetic biology techniques for developing vaccines, treating infectious diseases, and curing cancer.

Disease mechanism investigation

Immunological Disorders

The development of disease models and the identification of novel therapeutic targets are made possible by synthetic biology. (Pritchard *et al.*, 2012) [24]. It was possible to find new self-antigens (auto antigens) that could cause autoimmune disorders thanks to the synthetic display of the whole human peptidome on the surface of the T_7 phage. The Enrichment of auto antigens was carried out using antibodies from patients with neurological syndromes. After being exposed to high-throughput sequencing, the enriched antigens were found to contain novel antigens that might be exploited to create new medicines and precise diagnostic tests. (Ferrari *et al.*, 2007) [8].

Genome editing tools for cancer study

Gene therapy and disease modelling are using more and more genome editing technologies, such as zinc finger nucleases (ZFN), transcription activator-like nucleases (TALEN), and clustered regularly interspaced short palindromic repeats (CRISPR) in combination with the Cas9 nuclease (CRISPR/Cas9 system). (Cai, *et al.* 2014, Gaj, *et al.* 2013, Pan, *et al.*, 2013) [3, 11, 21]. These genome editing methods typically work by creating a double strand break that is specific to a sequence, which is then repaired by either the risky non homologous end joining (NHEJ) or homologous recombination (HR) routes. The latter approach allows for gene segment substitution or site-specific gene knock-in, whereas the former pathway only allows for the knockout of the desired gene. TALENs and CRISPR/Cas9 technologies have been crucial in modelling and drug target development because of their outstanding precision and relative ease of design, especially for a complex group of diseases like cancer. Additionally, chromosomal translocations related to cancer, such as those seen in Ewing sarcoma and anaplastic large cell lymphoma, have been modelled using ZFN and TALEN technology (Piganeau *et al.*, 2013) [23].

Drug discovery and production

Discovery

There is a growing need for new antibacterial chemicals as multi-resistant diseases become more prevalent. Synthetic biology-based techniques are in demand as a result of the recent decline in the number of new medications being discovered. For example,

Synthetic mammalian gene circuit was utilized for the discovery of novel anti tuberculosis compounds

Increased the sensitivity of *M. tuberculosis* to ethionamide. (Weber *et al.*, 2008) [8].

Discovering novel anticancer agents

Cytotoxic anticancer medications are more generic than "targeted" anticancer drugs because they selectively kill actively dividing cells by targeting DNA replication, which is thought to help them distinguish between malignant and normal tissues (Gonzalez-Nicolini *et al.*, 2005) [12].

Drug Production

Natural remedies have proven to be effective in treating conditions including oncology and viral disorders. (Baker *et al.*, 2007) [1] However, because these medications are generated in small quantities in native hosts, it is frequently uneconomical or potentially harmful to the environment to extract them from native hosts. Drug manufacturing in metabolically engineered microbes or plant cells, which can be made capable of mass production, is a potent remedy. (Lee *et al.* 2009, Mora-Pale *et al.* 2014, Keasling *et al.* 2010) [17, 20, 16].

Vaccine development

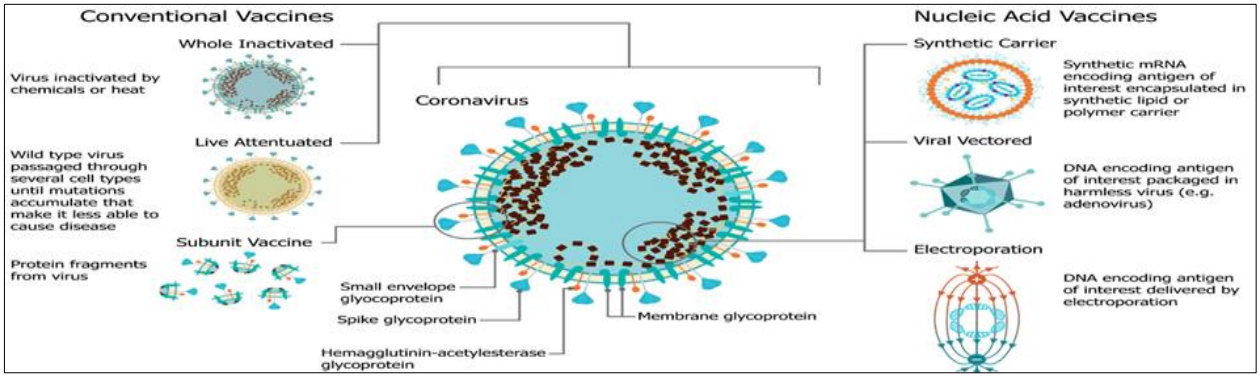


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Fig 3: Procedure of vaccine development

Another intriguing method for developing vaccines is the reengineering of viruses. By recoding the poliovirus capsid protein with underrepresented codons and creating the recoded DNA from scratch, the poliovirus was artificially attenuated. The poliovirus was attenuated in mice as a result of poliovirus recoding, which also decreased protein translation rates. The attenuated virus elicited a powerful immunological response in mice, suggesting that virus attenuation via codon de optimization might offer a different approach to the creation of vaccines. (Coleman *et al.*, 2008) [5]. Synthetic biology has been embraced by vaccine makers, according to Richard Kitney, PhD, a professor from Imperial College in London, who cites Moderna and Pfizer-Bio N Tech's mRNA COVID-19 shots as examples.

"Both vaccines were designed and implemented using synthetic biology techniques," he tells *GEN*. "With these vaccines it was possible to design them to specifically mimic the virus at the molecular level and hence to provide to the body's immune system with a direct template to which the immune system could react."

Treatment of infectious diseases

The nearly 100-year-old concept of using bacteriophages to treat bacterial infections is being revived by synthetic biology in response to the growing worry over bacterial medication resistance. (Henry *et al.*, 2012) [14]. The M13 phage was developed as part of a phage-drug combination therapy to boost the potency of antibiotics. LexA3, a regulator of the SOS response in *E. coli*, was changed in the phage. By blocking the SOS response, LexA3, which has also been shown to limit the development of antibiotic resistance, was anticipated to enhance bacterial killing by bactericidal medicines. The study showed that the modified phage significantly increased the survival of infected mice *in vivo* and significantly increased the bactericidal efficiency of a quinolone drug *in vitro*. (Lu *et al.*, 2009) [18]

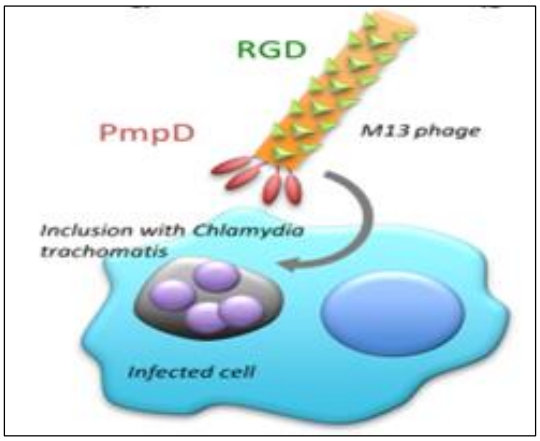

Fig 4: Engineering bacteriophages against pathogenic bacteria. M13 phage was engineered for enhanced mammalian host cell internalization by fusing two functional peptides, RGD and Pmp D, to the coat proteins of the phage. (Bhattarai *et al.*, 2012) [2]

Treatment of bacterial infections by commensal bacteria

Reducing the pathogenicity of dangerous bacteria with prophylactic consumption of manufactured commensal microbes is another intriguing synthetic biology method. The quorum sensing mechanism of *Vibrio cholerae* was employed to regulate the spread of infection. Manipulating commensal microorganisms is a feasible strategy for the treatment of bacterial diseases. (Duan *et al.*, 2010) [6].

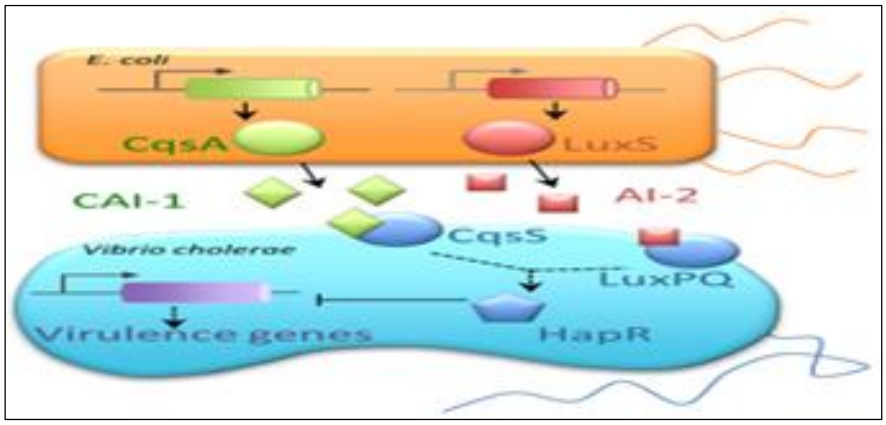

Fig 5: Engineering commensal bacteria against pathogenic bacteria. *E. coli* strain Nissle 1917 expressing auto inducer 2 (AI-2) was engineered to express cholera auto inducer 1 (CAI-1), both of which are molecules synergistically coordinating quorum sensing in *Vibrio cholerae*. Through a signal transduction cascade, CAI-1 and AI-2 inhibit the expression of virulence genes in *V. cholerae*. (Duan *et al.*, 2008) [7]

Cancer treatment

Oncolytic virotherapy

Although radiation and chemotherapy are frequently employed in clinics, their toxicity to cancer cells is very low since they frequently target non-cancerous tissues. Therefore, we need more advanced technologies that can distinguish between healthy and malignant tissues. Oncolytic virotherapy, which focuses on creating viruses that may infect and kill tumors, is one of the emerging technologies that may offer a solution. Naturally oncotropic viruses have been used as a starting point for the development of tumor-specific oncolytic viruses, as have viruses with tissue tropism. (Sze *et al.* 2013, Miest *et al.* 2014) [26, 19]. Through receptor targeting, which necessitates the alteration of receptor binding proteins, the selectivity for tumors can be tailored at the virus entry stage. To do this, single chain antibodies are often fused to the attachment proteins visible on the viral surface. (Verheije *et al.*, 2012) [27] However, tumour cells are capable of developing resistance through the target antigen's suppression or mutation. (Friedrich *et al.*, 2013) [10]. An oncolytic virus with bispecific targeting of tumour antigens was created to stop this process. This was made possible by the use of designed ankyrin repeat proteins (DARPins), synthetic antibodies that mimic single-chain antibodies but are smaller and less prone to aggregation. The measles viral attachment protein was fused with two distinct tumour marker-specific DARPins. The result was the creation of a virus with preserved oncolytic power and attenuated potency in non-target tissue. The multiplex targeting strategy may be useful in preventing the emergence of resistance in cancer cells. (Kaluza *et al.*, 2012) [15].

Designer Anticancer Bacteria

Another promising method for treating cancer is to engineer microbes to penetrate and kill cancer cells. In order to create even more potent anticancer bacterial strains, tumor-tropism and the capacity to kill cancer cells in *Salmonella*, *Clostridium*, and other genera have been demonstrated (Forbes *et al.*, 2010) [9].

Chimeric Antigen Receptors

It has been demonstrated that adoptive T cell treatment is successful in starting long-lasting antitumor responses (Pedrazzoli *et al.*, 2012) [22]. The function of redirected T lymphocytes depends on the presentation of tumour antigens by the major histocompatibility complexes (MHC), which are frequently blocked-in malignant cells. Chimeric antigen receptor (CAR) expression on T cells enables MHC-independent T cell activation and proliferation. (Han *et al.*, 2013) [13] (Chmielewski *et al.*, 2013) [4]. Mesothelin and a-folate antigens were engineered into dual-specific CAR-T cells, and this produced powerful action against a mouse xenograft model of ovarian cancer. These experiments demonstrated the effectiveness of creating CAR-T cells with two distinct targets to reduce parallel reactivity against normal tissues bearing a single antigen. (Sadelain *et al.*, 2009) [25].

Conclusion

Synthetic biology provides a lot of promise for the creation of next-generation therapies while being a relatively new field.

Many human problems are not solely genetic, even if conventional genome engineering techniques may be able to treat some genetic disorders. Therefore, complex illnesses like cancer, metabolic problems, viral diseases, and many other well-known diseases are much more complicated than they need to be treated by a straightforward genetic correction.

The creation of more potent therapeutic solutions than those now found in clinics requires sophisticated tools, including those suggested by synthetic biology.

However, this discipline is constantly expanding because to the creation of more affordable gene synthesis techniques, cutting-edge genome engineering tools, and continued work on functional sections. Despite recent advancements, synthetic biology still has a long way to go before it can be used in medicine.

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