Institute on Science for Global Policy

Synthetic Biology: A New Weapon in Our War Against Infectious Diseases**

John I. Glass, Ph.D.
Professor, J. Craig Venter Institute

Summary

Prior to the modern age, infectious diseases were the principal cause of human morbidity and mortality. The invention and widespread use of vaccines and antibiotics, along with advances in public health, sanitation, and nutrition, expanded human lifespan. Nevertheless, a variety of recent changes in society have increased the infectious disease burden globally. Although the discovery of new antibiotics has become more difficult, and the cost and time to licensure of new vaccines has increased, advances in biology offer possibilities for mitigating infectious diseases. Synthetic biology is a new field that engages in the design and assembly of genes and chromosomes from chemically synthesized DNA to create cells with properties unobtainable by conventional methods. It is already providing new ways to produce antibiotics and vaccines. Future advances in methods for DNA synthesis will make experimentation using synthetic bacteria and viruses less expensive and faster. This technology will enable the creation of vaccines based on rationally designed bacteria and viruses. Unfortunately, this technology could also enable bioterrorism. Recent construction of a bacterial cell with a synthetic genome showed that it currently would be too difficult for bioterrorists to synthesize bacterial pathogens; however, the use of synthetic biology to construct viruses is vastly easier. Still, the potential benefits of synthetic biology far outweigh the risks.

Current realities

In 1967, United States Surgeon General William Stewart wrote to Congress, “It is time to close the book on infectious diseases.” If only that statement were true. It was made at a time when antibiotic drug discovery and vaccine development were in their heyday. Advances in public health such as nutrition, insect control, and water and sewage treatment all made the elimination of infectious diseases seem possible. In hindsight, such optimism seems naive.

Today our view of infectious diseases is quite different. We have new and emerging disease agents, such as HIV. Although existing drugs still work in most cases, pathogens have evolved resistance mechanisms for all current antibiotics. Old scourges like tuberculosis (TB) have emerged in multidrug-resistant forms that defy all treatment. New phenomena, such as an aging population, increasing numbers of immunocompromised patients, and rapid international travel, increase vulnerability to infectious disease. New antibiotic development, which peaked in the 1980s, has slowed greatly. Many pharmaceutical companies have abandoned infectious disease research because of a failure to find new antibiotics in their chemical libraries, and the realization that development of resistance to new antibiotics would render them ineffective prior to patent expiration. Vaccines are now also becoming less effective because of another kind of resistance: the myth that all vaccines are dangerous. This distrust of vaccines has resulted in the avoidance of immunization and increased susceptibility to pathogens previously under control, which has triggered new epidemics.

Nonetheless, even though the war against infectious diseases may never be won, scientific advances continue to enable development of new weapons to combat pathogens. Genomics (i.e., reading and understanding DNA sequences) and synthetic biology are fields that provide insight into how an organism functions by reading its genetic code and enabling large-scale genetic remodeling via synthesis of genes and genomes. Biological experimentation provides insight needed to build new organisms and viruses that can be used to solve human problems.

The J. Craig Venter Institute (JCVI) Synthetic Biology Group is using synthetic biology to accelerate and improve the manufacture of influenza virus vaccines. One of the greatest threats to public health would be the emergence of a new pandemic strain of influenza virus that could claim millions of lives before a vaccine can be made. Because the virus is constantly evolving, every influenza season requires a new vaccine to be designed and produced based on the most important circulating viral strains. Every year, vaccine makers begin a six-month race to produce hundreds of millions of doses of vaccine. Advances in synthetic biology are about to enable a shorter time to development. Currently, virus production begins with the creation of a hybrid virus strain using classical genetics. Growth and isolation of a hybrid virus with the right mix of genes from two parental strains can take 35 days. Synthetic biologists have now developed a method to produce the exact virus needed for a vaccine in as few as five days. The key is rapid synthesis of a DNA copy of the influenza virus genome, which is transfected into mammalian cells to produce an actual virus.

Scientific opportunities and challenges

Advances in modern biology offer new solutions to some of the challenges posed by infectious diseases. In the near future, several developments in synthetic biology will likely lead to new approaches to prevent, mitigate, and control infectious diseases.

Low-cost synthetic DNA. Large DNA molecules, comprised of a few thousand nucleotide bases pairs to more than a million bases pairs, can currently be synthesized for about US$0.30 per base pair. In the near future, new technologies should decrease costs 10- to 100-fold. Similar reductions in the speed of synthesis should also occur. Rapid, inexpensive gene and genome synthesis will enable faster exploration of new options for developing therapies.

Synthetic vaccinology. Synthetic biology is already being used to produce vaccines more rapidly. It also offers solutions to challenges associated with vaccine development, such as product safety concerns, cost and time to clinical development, and design of vaccines against pathogens with high and shifting antigenic diversity. Synthetic biology can be used to synthesize small influenza viral genomes and, more impressively, has been used to create a bacterial cell with a fully synthetic genome. Currently, developing and licensing a new vaccine can take decades and almost US$1 billion. However, using synthetic biology methods, it may be possible to create viral and bacterial vaccine platforms in which only the immunizing antigens are varied. Once a basic vaccine platform is approved by regulatory agencies, subsequent versions of vaccines created using that licensed platform could be approved via streamlined clinical trials and be made in existing manufacturing facilities. Many of the most intractable vaccine targets, such as HIV and rhinovirus, are characterized by overwhelming antigenic diversity. Synthetic biology gives us the possibility of making multivalent vaccines in which a single attenuated organism or virus can evoke the production of various antibodies.

New chemical libraries. Almost all drugs are derived from a natural source. These chemical drugs are synthesized by clusters of genes dedicated to the production of a specific chemical. Many of these chemicals are used by the organisms to wage war on their neighbors. One of the surprises of genome analysis is that for every gene cluster producing a known metabolite, microbes contain 10 other metabolic clusters that we do not know what their product would be. Presumably, these gene clusters produce their metabolite only under specific unknown conditions. Synthetic biologists are now resynthesizing the elements of these gene clusters with each gene under the control of inducible promoters (i.e., gene triggers). These synthetic DNA modules are then inserted into organisms (e.g., bacteria) and induced to express the natural product. This approach will produce libraries of natural products that can be screened for useful activity. These will likely be rich sources of new antibiotics and anti-cancer drugs.

Risks and concerns about synthetic biology. In our post 9/11 world, with the advent of synthetic biology came increased concerns about bioterrorism and lapses in laboratory safety. This was especially true after the JCVI's announcement that a synthetic bacterial cell had been made. Although the public and governmental organizations have expressed concerns that the synthetic cell technology would lead to bioterrorists creating new untreatable bacterial pathogens, currently this technology is too expensive and difficult to pose a significant risk. However, the technology enabling the JCVI to more rapidly produce influenza virus vaccines could also be used to make viral pathogens. Disturbingly, a virologist/synthetic biologist could create polio virus, a pathogen no longer commonly immunized against, for less than US$5,000.

Policy issues

- **Reform intellectual property incentives for creating new antibiotics.** The pharmaceutical industry has largely abandoned infectious diseases research, especially for those diseases that principally infect the poor. The prospect of antibiotic resistance limiting the profitability of a new drug before its patent expires is a disincentive for developing new antibiotics. Intellectual property reforms may require revision of the current approach to patents. In exchange for new antibiotic creation, especially for diseases of the poor such as TB, drug companies could be rewarded with patent extensions on existing nonantibiotic drugs aimed at more affluent populations.

- **Decrease the regulatory burden for drugs and vaccines made using recombinant DNA technology.** In the U.S. and many other countries, genetically modified organisms (GMOs) and products produced using such organisms are subject to more stringent regulations than organisms and products made without recombinant or synthetic DNA. The U.S. regulatory framework for GMOs, often involving multiple agencies, creates a disincentive to the use of this superior technology. Scientists need to explain to the public the relative risks of organisms produced using designed, as opposed to random (natural), mutations. The scientific community and policy makers in each nation should work together to develop consistent regulations.

- **Develop a scientifically literate public.** The anti-vaccine movement would not have found wide acceptance if society understood what constitutes scientific proof and had a basic knowledge about biology. It is the responsibility of policy makers, educators, and the scientific community to improve the public's scientific competence. Scientists should commit 1%–5% of their time educating the public and policy makers about science. This public education effort should be required of all scientific teams receiving public funding.

- **Require commercial DNA synthesizers to deny sale to unauthorized users of synthetic genes and oligonucleotides that could be used to synthesize pathogenic viruses and toxins.** Currently, some U.S. DNA producers screen orders to ensure that whole genes that could be used to make certain pathogens or toxin genes are not sold; however oligonucleotide orders that would enable pathogen or toxin synthesis should be screened as well. This should be a worldwide policy. Scientists, DNA manufacturers, and policy makers should convene to develop uniform policies in this regard. Permits to receive such DNA should go to certain groups.

*** A policy position paper prepared for presentation at the conference on Emerging and Persistent Infectious Diseases (EPID): Focus on Mitigation, convened by the Institute on Science for Global Policy (ISGP) October 23–26, 2011, at the University of Edinburgh, Edinburgh, Scotland.*