Synthetic biology: Researchers mass produce genes on a chip

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Imagine that the bricks used to build a house cost $1,000 each—building a home would be cost prohibitive. Similarly, the bricks to build living organisms—genes and genetic assemblies—can cost thousands of dollars to make in the lab, which is also cost prohibitive.
But now, scientists have developed a way to make the materials for genes on a microchip in mass quantities, for a fraction of the current cost.

The technology enabled scientists to make an important part of the genome for an E-coli bug, and to reproduce the instructions for making proteins. This has significant applications in vaccine production, gene therapy, and DNA sensors and diagnostics.

"The significance of our paper is that for the first time, we have a mechanism for us to make the genes in high accuracy, very inexpensively, and to make those genes containing the information for the protein factory in an organism" that synthesize all other proteins in the body, said Erdogan Gulari, a University of Michigan professor, the Donald L. Katz Collegiate Professor of Chemical Engineering and co-author of a paper on the topic to appear in the Dec. 23 Nature. "This is the starting point to making a complete functioning organism that can produce energy, neutralize toxins, and produce medically useful proteins, for the benefit of human health and quality of life."

The paper, entitled "Accurate multiplex gene synthesis from programmable DNA microchips," was co-authored by researchers from

the U-M College of Engineering, Harvard University, University of Houston and Atactic Technologies Inc. The technology is currently licensed to Atactic, a company founded by a U-M College of Engineering alum Xiaochuan Zhou, professors Xiaolian Gao of University of Houston, and Gulari.

If made the standard way, a typical gene can cost several thousand to hundreds of thousands of dollars, Gulari said. That's because the cost of putting together each nucleotide, the building block of DNA and RNA, comes to $2 to $7 dollars each. Genes contain thousands to tens of thousands of oligonucleotides, short chains of nucleotides that join together to make genes. So synthesizing all the genes of even the most primitive living organism, which has several thousands of genes, could cost millions of dollars and take years, Gulari said.

The new method uses technology similar to that used to make computer chips, Gulari said, and generates oligonucleotides in thousands of tiny reaction wells and releases the sequences synthesized, Gulari said.

Scientists start with a thumbnail-sized silicon or glass chip containing microchannels and microwells loaded with low-cost reagent. The wells are so tiny, Gulari said, that thousands of them can be filled by half a drop of water. By shining tiny pixels of light at selected areas on the chip in a predetermined manner, scientists made thousands of gene fragments of specific sequences each containing 30-70 nucleotides. They then collected them in a solution microtube, and stitched them together in the desired order to produce the genes by enzymes.

The benefits of synthetic genes are tremendous, Gulari said.

"For instance, these products can be used to improve DNA sensor and diagnostics for comprehensive and more sensitive genetic analysis, and to produce the blueprint for novel proteins," Gulari said. "Some of these

proteins would be too toxic to obtain from natural sources, so the synthetic version is much safer. Some of these man-made proteins have novel functions which do not exist in nature, which potentially can be a new generation of vaccines or therapeutics."

For instance, Gulari said, 50 percent of drug molecules are based on proteins and antibodies, and there are over 371 new products currently in clinical trials targeting more than 200 diseases. Consequently, there is great interest in creating humanized antibodies for early detection of infection and for medicines. For these applications, millions of new proteins and antibodies must be tested, he said. This technology makes that possible.

A forerunner to the synthetic gene was the birth of recombinant DNA (the joining of DNA from different species and subsequently inserting the hybrid DNA into a host cell) about 30 years ago. Recombinant DNA, Gulari said, has become an indispensable tool for advancing biochemical and biomedical sciences for improving health care and disease treatment. Without recombinant DNA technologies, there wouldn't be insulin, alpha interferon (cancer drug), a hepatitis B vaccine, and many human growth hormones and other therapeutic proteins, he said.

The U-M College of Engineering is ranked among the top engineering schools in the country. Michigan Engineering boasts one of the largest research budgets of any public university, at $135 million for 2004. Michigan Engineering has 11 departments and two NSF Engineering Research Centers. Within those departments and centers, there is a special emphasis on research in three emerging industries: Nanotechnology and integrated microsystems; cellular and molecular biotechnology; and information technology. The College is seeking to raise $110 million for capital building projects and program support in these areas to further research discovery. The CoE's goal is to advance academic scholarship and market cutting edge research to improve

public heath and well-being.

Source: University of Michigan