TECHNOLOGY

Making more genes, better and for less

Methods for large-scale, high-quality gene synthesis at an affordable price are needed for advances in both synthetic biology and biotechnology. Two recent studies, both led by the group of George Church, describe new approaches to DNA synthesis that provide steps towards this goal.

One limitation for gene synthesis is the cost of making the oligonucleotides that are stitched together to make genes. Synthesizing oligonucleotides on DNA microchips has the potential to greatly increase throughput — and therefore reduce cost — compared with current methods in which oligonucleotides are made on columns. However, microchip-based synthesis results in complex mixtures of oligonucleotides, which leads to difficulties in assembling gene fragments and potential cross-hybridization between assembled fragments.


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Kosuri and colleagues avoided these problems by using primers that allow the specific amplification of only the oligonucleotides needed for the assembly of a particular gene. Following amplification and removal of the primers, genes were assembled by PCR and the resulting constructs were characterized. The authors showed that error-free genes could be made efficiently, even for antibody chain genes that had previously proved difficult to synthesize. They estimate that using this approach to DNA synthesis would bring the cost down to US$0.01/bp, compared with US$0.20/bp for current methods.

In a second paper, Matzas and colleagues describe how next-generation sequencing technology can improve the quality and scalability of synthetic DNA production, potentially using any source of oligonucleotides. Here, pools of oligonucleotides are pyrosequenced to identify DNA clones with a specific sequence. Clones are then picked off the sequencing platform and used for subsequent gene assembly, avoiding the need for any other selection steps. This approach is extremely high-throughput, potentially allowing millions of fragments to be sorted in a single run. Importantly, the selection of specific sequences also reduces the number of errors caused by inaccuracies in the input DNA, resulting in an estimated 500-fold improvement in accuracy when using microarray-generated oligonucleotides.

Approaches such as these should ultimately allow more widespread and economical construction of synthetic genomes and the production of large gene libraries, which could be used for the expression of enzymes and antibodies in the biotechnology sector.

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ORIGINAL RESEARCH PAPERS Kosuri, S. *et al.* Scalable gene synthesis by selective amplification of DNA pools from high-fidelity microchips. *Nature Biotech.* 28 Nov 2010 (doi:10.1038/nbt.1716) | Matzas, M. *et al.* High-fidelity gene synthesis by retrieval of sequence-verified DNA identified using high-throughput pyrosequencing. *Nature Biotech.* 28 Nov 2010 (doi:10.1038/nbt.1710)