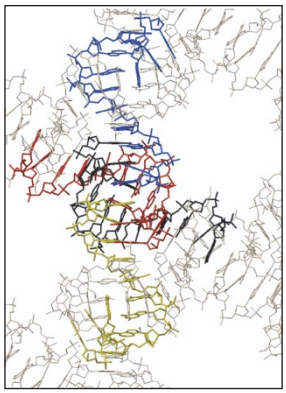
DNA building blocks



DNA has been used to assemble diverse nanometer-scale structures, including cubes, Borromean rings and tiled sheets. Now scientists have created a three-dimensional DNA lattice. Seeman, Paukstelis and colleagues found that a 13-mer DNA oligonucleotide designed to cocrystallize with a complementary oligonucleotide crystallized out of the mixture alone in the form of a lattice with spacious solvent channels. One potential application of a DNA lattice is to crystallize difficult-to-crystallize proteins in order to solve their structures. The channels in the 13-mer lattice are large enough to hold peptides or small molecules. To make a lattice that could accommodate proteins, the authors applied structural principles gleaned from the 13-mer lattice to model a lattice with much larger channels. Crystals of the larger lattice have not yet diffracted to sufficiently high resolution, although the size of the unit cell has been confirmed. The authors also tethered small molecules to the 13-mer oligonucleotide and produced crystals, but the small molecules were disordered and could not be seen in electron density maps. Other possible applications of DNA lattices include molecular sieves and electronic devices. (*Chemistry and Biology* **11**, 1119–1126, 2004) *KA*

DNA-go-round synthesis

Over evolutionary time, new biological molecules are created via an iterative process consisting of the generation of potential diversity through the emergence of new or mutated nucleic acid sequences, their expression and their selection for compounds with favorable characteristics. It is this exact process that Liu and colleagues try to emulate *in vitro* with their DNA-templated organic synthesis approach. The authors establish a single-solution library of DNA templates linked to a lysine derivative, which is subjected to three consecutive rounds of amine acylation reactions with building blocks made up of amino acids linked to DNA oligonucleotides. This process, which is analogous to protein synthesis, results in the generation of macrocycles that can be screened for a desired specific activity. In this case, the authors use the approach to select for a macrocyclic fumaramide that binds to carbonic anhydrase. After each round of selection, the DNA templates of the bound macrocycles are amplified, resulting in enrichment of the macrocycle with the highest affinity. This approach should prove useful to generate and select complex DNA-templated synthetic libraries of high structural diversity. (*Science* 305, 1601–1605, 2004) ***GTO***

Ribozyme redux

Mulligan and colleagues have designed a mammalian gene-regulation system based on *cis*-acting ribozymes and small-molecule ribozyme inhibitors. Although self-cleaving ribozymes are known to reduce the level of transcripts in which they are embedded, this process has never been efficient enough to exploit for gene regulation. The authors identified ribozymes with high self-cleavage activity using a combination of screening and rational modification. When properly positioned in an expression vector, the ribozymes substantially decreased reporter-gene expression in mammalian cells. Screening was also used to identify molecules that inhibit ribozyme activity and allow protein synthesis to proceed. The most potent of these inhibitors, the nucleoside analog toyocamycin, increased reporter gene mRNA to a level comparable to that seen with a control construct containing an inactive ribozyme. Finally, the authors demonstrated *in vivo* gene regulation using luciferase-expressing AAV vectors injected in mice. This new gene-regulation approach may prove advantageous for regulated delivery of protein therapeutics. (*Nature*, published online 23 September 2004, doi:10.1038/nature02844) *NC*

Research Highlights written by Kathy Aschheim, Nadia Cervoni, Gaspar Taroncher-Oldenburg and Mark Zipkin.

Deciphering gene regulation

Young and colleagues have mapped the transcriptional regulation system of yeast by analyzing transcription-factor binding across the genome in yeast grown under multiple conditions. First they used high-throughput chromatin immunoprecipitation and microarray experiments to determine the promoter regions bound by 203 transcription factors—nearly all transcription factors encoded in the genome—when yeast are grown in rich media. Similar experiments were done with a subset of these transcription factors for 1–12 additional growth conditions. The authors then applied computational methods to identify the precise sequences bound within the promoters. After refining these results using statistical analysis, a requirement for motif conservation across several *Saccharomyces* species, and information from the literature, they arrived at a final list of sequence motifs bound by 102 transcription factors. These motifs were mapped onto the genome sequence, revealing the global architecture of binding sites. By comparing how a large number of transcription factors bind under multiple growth conditions, the authors uncovered four common patterns of transcription-factor behavior. These results provide a framework for understanding the regulation of gene expression at the system level. (*Nature* 431, 99–104, 2004) ***KA***

One virus, two viruses, three viruses…

Rapid and specific detection of viruses is essential for enacting a quick and effective response to viral infections in humans. Existing methods often require time-consuming and risky manipulation of biological samples as well as relatively large amounts of samples. Lieber and colleagues now report that antibody-coated, optimized, semiconducting nanowires can successfully detect single viral particles in body fluid samples by conductance measurement, a feat not previously demonstrated using this type of device. The nanowires, which effectively function as field effect transistors, allow single influenza A virus particles to be detected by changes in conductance generated by virion binding and unbinding to the antibodies. Because the sensors are highly selective for specific virus particles, they could be applied to the parallel detection of several viruses or virus mutants. The approach should find extensive use in medical monitoring devices and could eventually be adapted to the detection of single molecules. (*Proc. Natl. Acad. Sci. USA*, published online 13 September 2004, doi: 10.1073/pnas.0406159101) *MZ*