the thermophilic bacterium *Termotoga maritima* (TM0449) (*2*) shows that the lack of similarity with ThyA extends to the tertiary structure and supports the flavin-dependent mechanism for thymidylate biosynthesis (see the figure). Strikingly, bound flavin adenine nucleotide (FAD) cofactor fortuitously cocrystallized with the protein in each of the four equivalent putative active sites of the ThyX homotetramer. The FAD-binding residues are highly conserved in the ThyX family, indicating that FAD is almost certainly a genuine cofactor rather than a crystallization artifact. The catalytic group of the cofactor faces a pocket that contains additional conserved residues including the essential serine. There is likely enough room in this pocket to accommodate both substrate molecules simultaneously. Similar to the classic thymidylate synthase ThyA (*5*), some of the ThyX conserved residues are in a flexible region of the putative active site that probably becomes ordered upon binding of substrate molecules. Apart from the intrinsic flexibility, the active-site structures of alternative and classic thymidylate synthases are not similar. This should allow design of specific inhibitors of ThyX that have no or little effect on the human ThyA enzyme. In contrast, drugs against ThyA must exploit subtle differences between the microbial and human enzymes. Unfortunately, the huge wealth of structural data available on the classic thymidylate synthase (about 100 structures for the enzymes from eight different organisms) will be of limited help in understanding the molecular mechanism of the alternative enzyme.

Since ThyA and ThyX lack both sequence and structural similarity, they likely evolved independently. This raises the intriguing possibility that both enzymes predate the origin of DNA itself. Alternatively, ThyX may have evolved more recently and displaced ThyA from many genomes because of its redundant function. Indeed, the sporadic phylogenetic distribution of *thyX* genes suggests a complex evolutionary history with multiple lateral transfers and nonorthologous displacements of *thyA* genes. Although ThyX has no significant similarity to any known protein structure, a functionally related enzyme with a similar mechanism has been described previously (*6*). Ribothymidyl synthase from *Streptococcus faecalis* methylates a particular uridine in transfer RNA using CH_2H_4folate and $FADH_2$. No sequence information is available on this enzyme, but the genome of the bacterium, now known as *Enterococcus faecalis*, has been sequenced completely (*7*) and presumably contains the gene for ribothymidyl synthase.

Elucidation of the function and mechanism of ThyX highlights the importance of contributions from bioinformatics and structural genomics to the functional genomics effort. But there is also a wealth of data from biochemical and genetic studies of the pregenomic era. There are examples of enzymes with known function, but no sequence information linking them to genes. The challenge is to integrate all of this information so that the full potential of genomic research is realized.

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PERSPECTIVES: NANOTECHNOLOGY

Tools for the Biomolecular Engineer

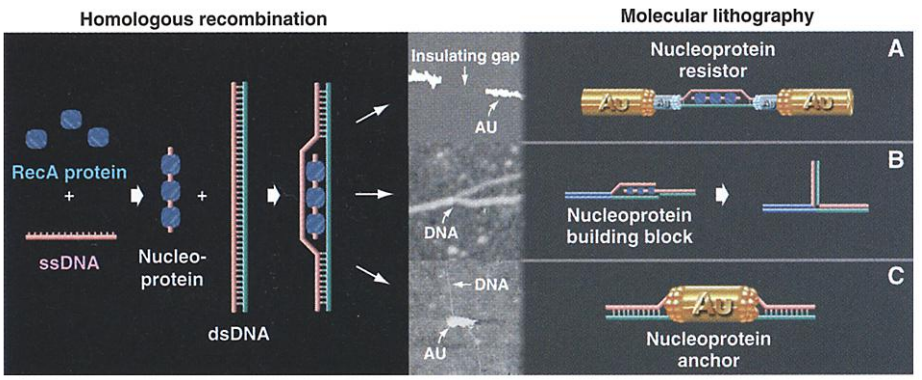
Christof M. Niemeyer

The electronics industry has continuously increased the speed and complexity of devices. Moore's law, the doubling of transistor density on integrated circuits every year, has held approximately true until today (*1*). It is widely accepted, however, that a further reduction in the size of interconnects and components can hardly be achieved by conventional "top-down" methods (such as photolithography), but rather requires fundamentally new approaches for the fabrication of electronic parts. "Bottom-up" technologies based on the self-assembly of molecular building blocks to form larger functional elements are being explored as potential ways to fabricate nanometer-size devices (*2*).

Biomolecules are particularly promising components in self-assembly processes, because their binding capabilities have been tailored to perfection by billions of years of evolution (*3*). For example, DNA oligonucleotides have unique and predictable recognition capabilities due to the specificity of Watson-Crick base-pairing, making DNA a promising construction material for growing well-defined nanostructures. Furthermore, nucleic acids can be processed with angstrom-level accuracy with enzymes, such as nucleases and polymerases.

DNA has already been used to fabricate complex nanostructured architectures (*4*). In this issue, on page 72, Keren *et al.* describe an exciting "molecular lithography" approach (*5*) that further increases the scope of using DNA as a template for the wet-chemical growth of basic electronic parts.

In prior work, DNA has been used to grow conductive, wirelike elements (*6*).



Learning from nature. Homologous recombination, a biological process that enables the specific combination of two DNA molecules (**left**), has been harnessed for the bottom-up fabrication of basic electronic parts by means of molecular lithography (**right**).

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Keren *et al.* increase the complexity of such devices by using yet another biomolecule, the RecA protein, which plays a major role in genetic recombination of the cell. Multiple RecA proteins polymerize at a single-stranded DNA (ssDNA) molecule. By homologous recombination, the resulting DNA-protein complex recognizes and binds to the complementary target sequence present in double-stranded DNA (dsDNA). Keren *et al.* treat the DNA-protein complex with silver ions, which are reduced by aldehyde groups previously generated in the dsDNA target. The resulting small silver grains are later used for the wet-chemical deposition of gold.

This procedure leads to the formation of a conductive wire, with an insulating gap precisely at the position where RecA was bound (see panel A in the figure). The information encoded in the DNA molecules thus replaces the masks used in conventional lithography, while the RecA protein serves as the resist. This approach should, in principle, work with high resolution over a broad range of length scales from nanometers to many micrometers.

Molecular lithography also enables the generation of branchpoints (three-way junctions) in linear DNA fragments. This is accomplished with the use of a dsDNA fragment containing a single-stranded end in the initial RecA polymerization step (see panel B). Treatment of the DNA-protein complex with polymerase leads to the sequence-specific formation of a stable three-way junction, which can later be used for the fabrication of more complex components, such as three-terminal electronic devices. This clear demonstration of the feasibility of biomolecular construction is likely to trigger further efforts to design advanced host systems required for efficient in situ generation of nanostructured DNA networks, and for their site-specific attachment and connection with the macroscopic world.

Molecular lithography can also be used for the sequence-specific positioning of molecular objects (see panel C). To this end, the ssDNA used for polymerization of the RecA monomers is modified with molecular entities that are functional devices or allow for the binding of such devices. To illustrate this possibility, Keren *et al.* introduced biotin groups in the ssDNA, enabling the specific docking of streptavidin-coated gold nanoparticles that were later used for the growth of a metal island. This feature of molecular lithography should stimulate extensive follow-ups, taking advantage of previous work on the DNA-directed assembly of metal and semiconductor nanoparticles (*7*) and/or proteins (*8*).

Additional perspectives for molecular lithography may be opened by incorporating novel proteins obtained by molecular biotechnology techniques, such as directed evolution and phage-display. These approaches have already allowed the in vitro production of protein linker units that recognize semiconductor quantum dot surfaces (*9*). The linkers can thus be used to assemble individual nanometer-size inorganic particles into two- and three-dimensional superstructures.

The combination of molecular lithography and protein bioengineering should open up ways to generate and integrate supramolecular nanoparticle networks and microelectronic devices with biomaterials that possess distinct functionality with respect to enzymatic activity and redox properties (*10*). The highly evolved catalytic turnover of many enzymes and the mechanical or electronic transduction properties of, for example, motor proteins, oxidoreductases, and ion channels, should enable new applications in the areas of sensing, catalysis, and electronics. The joint venture of biotechnology and electronic engineering promises plenty of excitement from future developments.

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PERSPECTIVES: CANCER

Addiction to Oncogenes—the Achilles Heal of Cancer

I. Bernard Weinstein

A single cancer cell frequently contains mutations in multiple genes, gross chromosomal abnormalities, and widespread changes in its gene expression profile. An axiom in cancer research is that the multistage process of tumor formation (*1*) is driven by progressive acquisition of activating mutations in dominant growth-enhancing genes (oncogenes) and inactivating mutations in recessive growth-inhibitory genes (tumor suppressor genes) (*2*). Epigenetic (nonmutational) abnormalities leading to increased or decreased expression of these genes, respectively, are also important for tumorigenesis (*2–4*). Since the discovery of oncogenes about 20 years ago, more than 100 oncogenes and at least 15 tumor suppressor genes have been identified, and the list keeps growing. Oncogenes and tumor suppressor genes are important not only for cell proliferation but also for cell fate determination (differentiation, senescence, and apoptosis), their effects often depending on the type of cell in which they are expressed. Thus, overexpression of a given oncogene can enhance growth in one cell type but inhibit growth or induce apoptosis in another (*2–4*).

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A tantalizing question still under debate is whether an oncogene that is crucial for the initial development of a specific tumor is required for maintaining the malignant phenotype of that tumor. The study by Jain *et al.* on page 102 of this issue (*5*) addresses this question. By unraveling the molecular circuitry that maintains the biologic properties of cancer cells, we will be better able to predict selective molecular targets for cancer therapy. Jain and colleagues (*5*) engineered a conditional transgenic mouse to overexpress the *myc* oncogene, which induced formation of highly malignant osteogenic sarcoma. They discovered that brief loss of *myc* overexpression caused the tumor cells to differentiate into mature osteocytes that formed histologically normal bone. It is also intriguing that subsequent reactivation of *myc*, rather than restoring tumor growth as would be predicted, instead induced apoptosis of the tumor cells.

These findings are consistent with other data showing that cancer cells are often "addicted to" (that is, physiologically dependent on) the continued activity of specific activated or overexpressed oncogenes for maintenance of their malignant phenotype. For example, Felsher and Bishop (*6*) showed that transgenic mice expressing the *myc* oncogene in hematopoietic cells developed malignant T cell leukemias and acute myeloid leukemias. However, when this gene was switched off the leukemic cells underwent proliferative arrest, differentiation, and apoptosis. Pelengaris *et al.* (*7*) targeted expression of an activatable