such as water and OH at low latitudes on Mars.

It is particularly impressive that the three reports in this issue were generated after the Odyssey spacecraft had completed only ~30 days of its planned multiyear mission, and during a phase of the mission before the Gamma-Ray Spectrometer (GRS) had been deployed to its nominal mapping configuration. The GRS was originally flown to Mars on the Mars Observer spacecraft, which stopped working just 3 days before entering Mars orbit in 1993. Many Odyssey investigators have been waiting more than 15 years to finally collect these data. One can hardly blame them for their enthusiasm and excitement over their early findings.

Within the next few weeks, the GRS is to be extended out on a ~6-m boom (see the second figure) to isolate it from neutron and gamma-ray signals originating in the Odyssey spacecraft itself and thus boost the instrument's sensitivity to the surface of Mars. The results from that configuration are sure to provide additional insights into subsurface ice and surface hydrated minerals, and yield unique new information on the planet's geochemistry from global maps of rock-forming elements such as Fe, Si, and Mg. The results will also be used to guide the selection of landing sites for future rovers and landers, to sample returns, and for eventual human exploration. In that sense, the most important implications of the detection of subsurface water ice deposits on Mars may not be realized for decades. It is likely to be worth the wait, however.

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PERSPECTIVES: BIOCHEMISTRY

DNA Building Block Reinvented

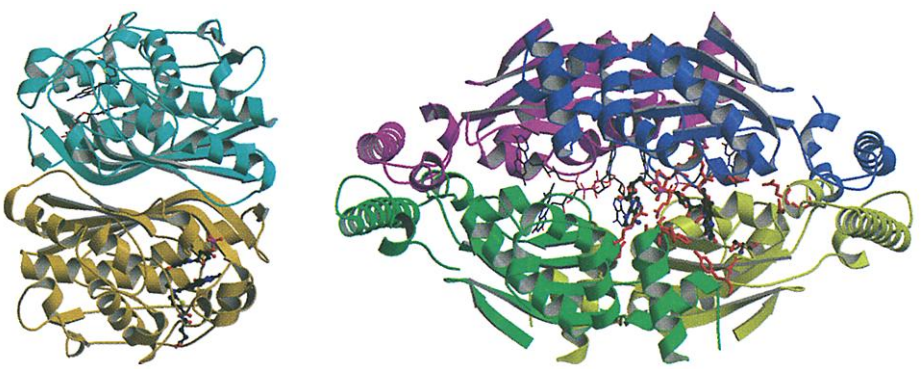
Alexey G. Murzin

The large number of complete genome sequences are fueling large-scale bioinformatics, structural genomics, and proteomics efforts that promise to accelerate the design of new drugs. But how often will independent projects converge to give functional and structural characterization of interesting drug targets? There is at least one example. On page 105 of this issue, Myllykallio *et al.* (*1*) identify a family of enzymes, ThyX (Thy1 in the slime mold *Dictyostelium discoideum*), that synthesize the essential DNA precursor thymidylate (dTMP) by an alternative pathway. ThyX enzymes are unrelated to the classic thymidylate synthase family ThyA, and ThyX is found almost exclusively in organisms that lack ThyA, including several microbial pathogens of humans. In an exciting coincidence of events, the structure of ThyX was independently determined by the Joint Center for Structural Genomics (*2*). Together these two discoveries pave the way for rational drug design (see the figure).

Given the universal role of DNA as the cell's genetic material, mechanisms for de novo synthesis of essential DNA precursors, like thymidylate, were thought to have evolved just once and thus to be conserved in all cellular organisms from bacteria to human. Surprisingly, about 25% of the 150 or so complete or nearly complete genome sequences lack detectable homologs of the classic thymidylate synthase gene *thyA*. Two observations suggest that ThyX might be an alternative thymidylate synthase. First, a *thyX* homolog from *D. discoideum* complements a thymidine-requiring mutant (*3*), and second, the phylogenetic patterns of ThyX and ThyA are complementary (*4*). Myllykallio and co-workers (*1*) found that *thyX* is distributed among many microbial genomes and is almost exclusively limited to genomes lacking *thyA*.

Myllykallio *et al.* (*1*) went on to show that ThyX from the human pathogen *Helicobacter pylori* (HP1533), the cause of gastric ulcers, has a thymidylate synthase activity both in vivo and in vitro that is mechanistically distinct from ThyA activity. In the classic mechanism, deoxyuridylate (dUMP) is reductively methylated by methylenetetrahydrofolate (CH_2H_4folate) to give thymidylate and dihydrofolate. Dihydrofolate must be recycled; first, it is reduced to tetrahydrofolate by dihydrofolate reductase (DHFR). Functionally coupled, both ThyA and DHFR are important chemotherapeutic targets. The alternative mechanism also uses dUMP and CH_2H_4folate but, in addition, it involves the oxidation of a reduced flavin cofactor to give thymidylate and tetrahydrofolate and, therefore, requires no DHFR activity. Consistent with this, DHFR homologs are absent from many of the ThyX-containing genomes. The catalytic centers in the enzyme remain to be definitively elucidated, but an invariant serine residue in a conserved "ThyX" motif is essential for ThyX activity (*1*).

A structure of a ThyX homolog from



The road less traveled. (Left) Structure of classical thymidylate synthase (ThyA). **(Right)** Structure of the alternative thymidylate synthase (ThyX). The bound ligands (the substrate and a drug in ThyA, and FAD cofactor in ThyX) show the active-site locations. Conserved ThyX residues (red) are shown in one site composed of three different subunits (yellow, green, and blue). The essential serine residue (ball-and-stick) occupies a catalytically relevant position near the flavin ring of the cofactor.

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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.

References and Notes

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PERSPECTIVES: NANOTECHNOLOGY

Tools for the Biomolecular Engineer

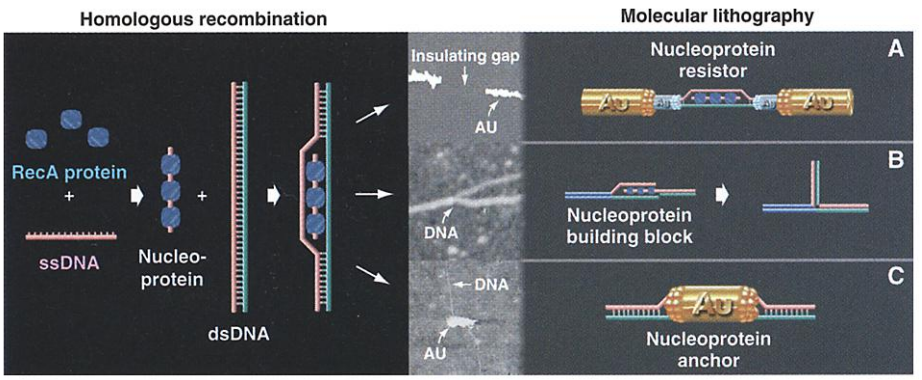
Christof M. Niemeyer

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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