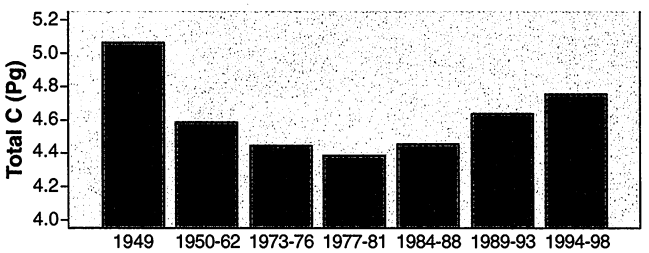
trol, to protect water supplies, and to produce wood for fuel. Reforestation and afforestation policies have reversed the sharp decline in Chinese forests (see the figure, this page). Planted forests now account for 20 percent of the total organic matter and 80 percent of sequestered carbon in China.

It is the past decisions on land use that drive $CO_2$ uptake by forests today in both the United States and China. But the policies of the two nations are very different in character and intent. In the United States, land use decisions are largely private matters driven by socioeconomic trends. Marginal agricultural land has been abandoned in the face of intensification and industrialization of agriculture. Timber harvesting has responded to market pressures. Fires have been suppressed to protect private and public property, with ambiguous long-term effects on atmospheric $CO_2$. For instance, increases in combustible material in fire-prone areas must be addressed lest conflagrations lead to disaster and, incidentally, to a rapid return of sequestered carbon to the atmosphere. In China, afforestation and reforestation are government policies intended to enhance forests, but were never intended to reduce the rate of increase in atmospheric $CO_2$. In neither country has sequestration of carbon been included as a factor in land use decisions.




**Boosting carbon stocks.** Changes in carbon stocks (the amount of sequestered carbon) in Chinese forests over the past half-century (*7*).

The reports by Pacala, Fang, and their colleagues help to demystify the low rate of accumulation of atmospheric $CO_2$. In addition, these authors demonstrate the potential benefits associated with managing forest resources not only for promoting traditional uses (production of fiber, flood control) but also for slowing the rise in atmospheric concentrations of $CO_2$. Forests cannot miraculously stop an increase in $CO_2$ in the atmosphere, but they can significantly mitigate the rate of increase for many decades to come. The opportunities are balanced by the risks of inaction or regressive policies that could promote the release of carbon currently stored in forests, halting or reversing the benefits of forests acting as carbon sinks.

These new studies on carbon sequestration help to provide the rationale for sensible national and international policies regarding forests and the $CO_2$ cycle. We need to develop a scientific basis for measuring and improving the properties of forest carbon sinks (*9*). The United States should join with other countries to provide sensible incentives for land use decisions, from the tropics to the boreal zone, that optimize the many benefits of forests, including their ability to sequester anthropogenic $CO_2$.

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PERSPECTIVES: MICROBIOLOGY

# The Great Escape

**Graham F. Hatfull**

Lytic bacteriophages are parasitic viruses that infect and replicate inside bacteria. But these skilful parasites face a conundrum: How can their progeny escape from bacteria so that they can go forth and multiply? Most bacteria are surrounded by a tough wall composed of a cross-linked peptide-sugar (peptidoglycan) matrix that protects the bacterial membrane and helps to maintain the microbe's shape (see the figure) (*1*). Building and maintaining this peptidoglycan matrix is problematic for bacteria because the wall must be strong enough to withstand the osmotic pressure from within yet flexible enough to be constantly remodeled as the microbe divides and grows. On page 2326 of this issue, Bernhardt and colleagues (*2*) report that some bacteriophages have adopted strategies to block enzymes in the peptidoglycan synthesis pathway, skillfully exploiting the bacteria's need to continuously synthesize these molecules.

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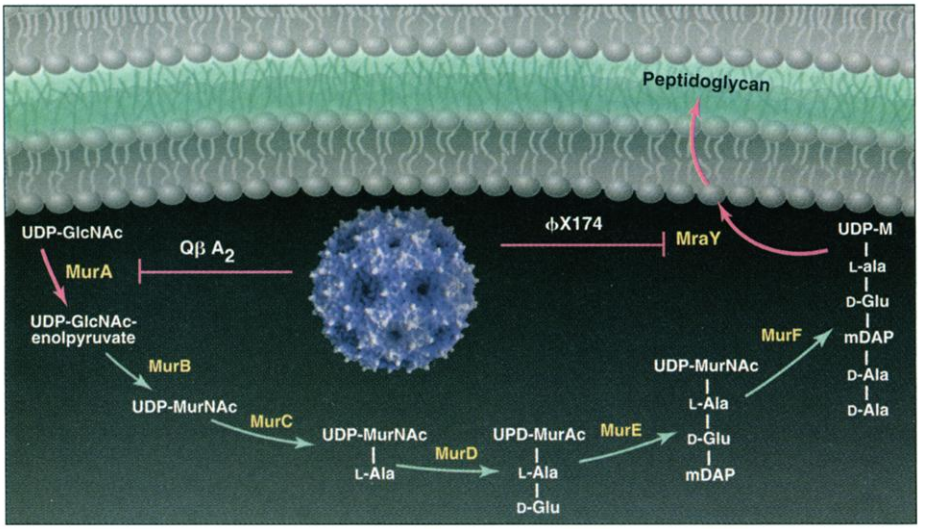
One obvious way to disrupt bacterial walls is to smash through them. Most double-stranded DNA phages exercise this option—they produce an endolysin that rips apart the peptidoglycan matrix. The bacterial membrane beneath the matrix, however, presents a barrier that separates these muralytic enzymes from their targets (see the figure). Undaunted, these phages also produce a holin protein that permeabilizes the membrane and lets the endolysin wrecking crew gain access to the peptidoglycan matrix (*3*). Lysis of the bacterial wall needs to be closely coordinated with virus replication and the assembly of viral progeny because premature rupture would be suicide for the phage offspring (*4*). As always, timing is everything.

According to Bernhardt and co-workers, lytic phages with smaller genomes, such as the RNA phage Qβ (*2*) and the single-stranded DNA phage φX174 (*5*), use a very different strategy for escaping from their bacterial hosts. These phages encode neither an endolysin nor a holin and have no way of attacking preexisting bacterial wall structures (*2*, *5*). Instead, they interfere with the bacterial enzymes that make precursors of the peptidoglycan murein, a key component of bacterial walls. The resulting lack of coordination between peptidoglycan synthesis and bacterial wall construction leads to weaknesses in the wall, which collapses owing to osmotic pressures from within.

Phage φX174 makes a single lytic enzyme, protein E, which is associated with the bacterial membrane (*6*). This lysin blocks the activity of MraY, a bacterial membrane protein that catalyzes the transfer of murein precursors to lipid carriers so that the precursors can be transported through the membrane. Phage Qβ does not encode a single protein with a dedicated lytic activity, but rather produces a multifunctional $A_2$ maturation protein. Present as a single copy in the capsid coat of the phage, this remarkable 41-kilodalton polypeptide is necessary not only for lysis of bacteria but also for binding of the bacteriophage to the bacterial sex pilus during infection (*7*).

Like protein E of phage φX174, $A_2$ specifically interferes with bacterial wall biosynthesis, but acts at an earlier stage by inhibiting the MurA enzyme. Bernhardt *et al.* (*2*) show that this inhibition is membrane-independent and appears to involve a direct interaction between $A_2$ and its MurA substrate. This is supported by their finding that $A_2$-resistant *Escherichia coli* mutants have a single amino acid substitution in a region on the surface of MurA that




**Phage antibiotics?** Some bacteriophages (blue) are able to lyse their bacterial hosts by blocking steps in the synthesis of murein precursor molecules, which are required for assembly of the bacterial peptidoglycan wall. A group of bacterial enzymes (MurA–MurF) converts UDP–*N*-acetylglucosamine (UDP-GlcNAc) into the final cytoplasmic precursor of murein, UDP-MurNAc pentapeptide. This precursor molecule is then linked to lipids in the bacterial membrane by the enzyme MraY. Protein E of phage φX174 inhibits MraY, whereas the $A_2$ capsid-associated protein of phage Qβ inhibits MurA.

presumably interacts with $A_2$. Intact Qβ virions specifically block MurA activity in vitro, presumably owing to the single copy of $A_2$ present in each Qβ particle. Finally, Bernhardt and co-workers detected the accumulation of UDP–*N*-acetylglucosamine (the substrate for MurA) in Qβ-infected cultures, confirming that $A_2$ does indeed block MurA.

The mechanism and timing of bacterial lysis by the $A_2$ protein of Qβ phage are not known. In vitro studies suggest that $A_2$ binds tightly to MurA, but because there are about 1500 copies of MurA per bacterium, bacterial wall construction will not be blocked until equivalent amounts of active $A_2$ have accumulated. An attractive possibility is that $A_2$ does not become active until it is assembled into viral particles, viral assembly itself being the trigger for lysis of bacteria—a neat solution to the timing problem.

Peptidoglycan biosynthesis is a multistep process dependent on many enzymes (*1*). Bacteriophages can select any of these bacterial enzymes as targets, although MurA and MraY are the only targets identified so far. It is likely that other small-genome phages will turn out to block additional enzymes in the peptidoglycan synthesis pathway of bacteria. Indeed, the product of the small-genome phage, MS2, appears to encode a protein, L, that inhibits another—yet to be defined—step in peptidoglycan biosynthesis (*2*). Doubtless, a hunt for more lytic small-genome phages will reward us with additional lysins that attack this bacterial underbelly.

Could these phage-encoded protein antibiotics be of therapeutic value? Bernhardt and colleagues like the idea and suggest that DNA-encoded oligopeptides that bind to enzymes in the murein synthetic pathway and inhibit bacterial wall construction could form a new class of antibiotics. Considerable support for phage-encoded lytic proteins as antibiotics comes from the demonstration that purified phage endolysin is highly effective in treating oral streptococcal infections in mice (*8*). The growing problem of antibiotic resistance among bacterial pathogens should speed the thorough exploration of this option. Given the enormous abundance of bacteriophages in the biosphere—estimated to be around $10^{31}$ particles (*9, 10*)—and the evident diversity of targets for bacterial lysis, bacteriophage lysins may represent a sizable untapped reservoir of new therapeutics.

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PERSPECTIVES: GENOMICS

# On Choosing Mammalian Genomes for Sequencing

**Stephen J. O'Brien, Eduardo Eizirik, William J. Murphy**

Fifty years ago, James Rettie proposed a graphic imagery (*1*) that made the geological time frame of biological evolution more comprehensible. Rettie imagined a time-lapse motion picture of Earth taken from space, beginning 757 million years ago, with one image being photographed each year. Projected at the normal speed of 24 images per second, the resulting movie would take a year to view, with each day representing 2.1 million years. Here is what the movie would show:

From January to March there is little sign of life, then the first unicellular microbes appear in early April, giving rise to small multicellular aggregates later that month. In May the vertebrates emerge, and by July land plants have begun to cover the globe. In mid-September early reptiles preview the dawn of the dinosaur era, which continues through late November, dominating the world for 70 days. Birds and small mammals first appear in early November but are overshadowed by reptilian species until 1 December, when the dinosaurs disappear abruptly. By late December the recognizable ancestors of modern families of mammals make their debut, but not until midday on New Year's Eve do our first ancestors appear. Between 9:30 and 10 p.m., *Homo sapiens* migrates out of Africa to populate Eurasia and the Americas. At 11:54 p.m., recorded human history and civilization as we know it begin. Mammals flourish for the last 50 to 60 days of the movie year, and humankind eventually appears during the final 12 hours of the last day of the year.

Today, some 4600 to 4800 species of mammals dominate the planet. They occupy every continent and diverse ecological niches. The morphological and physiological differentiation seen among mammals is enormous, ranging from blue whales to echolocation-driven bats, from blind subterranean naked mole rats to us. The richness of mammalian species diversity and

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