a building block and a ketosynthase (KS) domain adds it to the growing chain. The dimeric KS also contributes most of the dimer contacts in the complex.

The second key architectural feature is an open and flexible design that is ideal for insertion or deletion of catalytic domains, especially in the modifying wing. Each two-carbon addition (via malonate) to a fatty acid chain is followed by three reactions—keto reduction (KR), dehydration (DH), and enoyl reduction (ER)—carried out in the modifying wing of the FAS-I. A major source of chemical diversity in polyketides arises from deletion or inactivation of one or more of these modifying domains (see the figure, panel C), providing the chemical variation that is lacking in fatty acids.

In FAS-I and most fungal PKSs, the assembly line is used for iterative synthesis: Each enzyme domain performs the same reaction at each extension step on the growing substrate. In contrast, in most bacterial PKSs, polyketide synthesis is sequential: Each extension step is carried out by an individual FAS-I–like "module," offering the possibility to vary the building block identity and modification chemistry at each step. This scheme greatly expands genetic and protein complexity. Several modules (up to 20 or more) are required to build a complex polyketide, and specific interactions of sequential modules must be faithfully maintained by fusion or by docking domains (*7*, *8*).

A big surprise of the new FAS structure is a vestigial methyltransferase (MT) domain at the periphery of the dimer, following the DH in the polypeptide sequence. Thus, the megaenzyme ancestor of FAS-I appears to have had a methylation reaction as part of its fatty acid biosynthetic cycle. Was there a prokaryotic methyl branched-chain fatty acid, unknown to us today? The MT domain lost its function in FAS-I, was deleted from most PKS systems, but exists in some PKSs as an active methyltransferase. And herein lies a conundrum; the ubiquity of PKS pathways in bacteria and elsewhere strongly argues that the original FAS-I evolved in a prokaryote. However, other than *Mycobacterium tuberculosis* and related species that generate unusual fatty acids, we know of no modern prokaryote that uses a FAS-I for normal membrane lipid fatty acid biosynthesis (*9*).

In many PKS modules, the open FAS-I architecture has been augmented with a variety of other catalytic domains, such as *S*-acetyltransfer, halogenase, cyclopropanase, decarboxylase, and even entire NRPS modules (see the figure, panel D) (*10*, *11*). The new structure of the terminal module of the surfactin NRPS (*1*) shows how it, too, is highly adaptable. Like FAS-I, the NRPS has a solid platform for condensation, including an adenylation (A) domain to select the amino acid building block and a condensation (C) domain to form a peptide link to the growing chain (*1*). The monomeric C-A didomain (analogous to KS-AT in the FAS-I condensing wing) is fused to a PCP and a terminal TE domain. As in the FAS-I structure, the PCP is flexibly linked to the synthetase by tethers long enough for it to deliver substrate to the active sites of all catalytic domains. Unlike the FAS-I structure, the PCP and TE domains are well ordered in the NRPS module.

The three assembly line types use homologous domains (ACP or PCP) to carry the growing fatty acid, polyketide, or peptide via a pantetheine-linked thioester. The common thioester chemistry and the adaptable architecture have resulted in the proliferation of hybrid PKS-NRPS and even PKS-FAS-I pathways found in phylogenetically diverse bacteria (*9*, *12*). The rich diversity of PKS, NRPS, and hybrid systems demonstrates that nature has not employed a Henry Ford–like assembly line, from which the customer could have any color car so long as it was black. Rather, we see a modular assembly line that is easily copied, modified, and adapted to new function; this is the secret to its success.

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10.1126/science.1163785

MICROBIOLOGY

How to Infect a Mimivirus

Large DNA viruses such as the giant Mimivirus can be infected by smaller viruses.

Hiroyuki Ogata and Jean-Michel Claverie

The giant DNA "Mimivirus" (*Acanthamoeba polyphaga* mimivirus, or APM) was initially mistaken for a bacterium, until La Scola *et al.* classified it as a virus in 2003 (*1*). This highly unusual virus has more genes than many bacteria (*2*), forms the most complex known virus particle (*3*), has a unique DNA delivery system (*4*), and encodes aminoacyl-tRNA synthetases (*5*), normally restricted to cellular organisms. As a possible "missing link" between the cellular and the viral world, APM's discovery revived theories that link DNA viruses to the emergence of the eukaryotic nucleus (*6*). Large viruses closely related to APM are abundant in the sea (*7*) and may play important roles in the geochemical fluxes that regulate Earth's climate. La Scola *et al.* now report in *Nature* (*8*) that the APM family has another unusual property: It is susceptible to infection by another virus, named Sputnik (after "traveling companion" in Russian).

Sputnik—a small icosahedral virus with a DNA genome encoding 21 genes—was isolated with a new strain of APM from a cooling tower in Paris. Attempts to culture Sputnik alone in amoeba cells were not successful. However, when amoebae were inoculated with the two viruses, both Sputnik and APM virions multiplied. La Scola *et al.* (*8*) show that Sputnik reproduces in the "virus factory," the replication and assembly center built by APM in amoeba cells during their lytic infection. The virus factory is a DNA-rich cytoplasmic compartment that appears 4 hours after APM infection and grows to several micrometers in diameter. Sputnik virions reproduce faster than do APM virions; 6 hours after infection, Sputnik virions start to emerge from the virus factory, while the new generation of APM virions only appears after 8 hours. Infection with both viruses decreases the yield of infective APM virions

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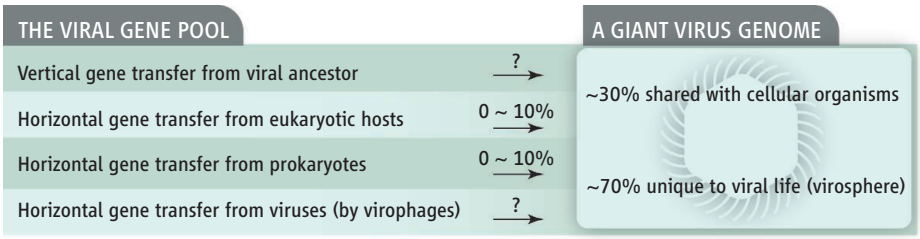

Origin of genes in large eukaryotic viruses. The distribution of sequence database matches suggests diverse origins for the genes of large DNA viruses. Horizontal gene transfer may occur through exposure to host or prokaryotic DNA. The many genes unique to viruses are vertically or horizontally transferred between viruses—a process in which the newly discovered virophages may play a key role.

and results in "sick" APM virions with aberrant morphologies. Sputnik thus behaves as a true parasite with a detrimental effect on APM reproduction.

Small viruses requiring other larger viruses for their reproduction have previously been documented. These "satellite viruses" lack essential functions for multiplication, for which they exploit their "helper viruses." La Scola *et al.* (*8*) argue that Sputnik is more than a satellite virus, because it uses its partner's virus factory and impairs its fitness. They therefore call Sputnik a "virophage."

What is the origin of the Sputnik virophage? The authors provide evidence suggesting the existence of related virophages in the oceans (*8*). Marine virologists have reported small viruses occurring with larger ones in marine protist populations (*9*, *10*). During recurrent infection of a cell by the two viruses, one virus may begin to benefit from the other. Like Sputnik, the small marine viruses multiply faster than the larger ones. If the viral genomes can physically interact, genes can be exchanged, and the two viruses may evolve into various states of dependency, from mutualisms to parasitism. In this context, it is worth noting that Sputnik has an integrase (an enzyme that inserts pieces of DNA from one DNA molecule into another). The genome of a marine virus, infecting the planktonic species *Emiliania huxleyi* contains a strange 176-kb central segment (*11*): Genes in this segment lack homologs in other viruses, but harbor a unique promoter. This segment is expressed much earlier than the rest of the viral genome and may be the integrated genome of an unknown virophage.

The genes in giant eukaryotic viruses have multiple origins (see the figure). The APM genome contains eukaryotic- or prokaryotic-like genes. Recent horizontal gene transfers from its eukaryotic hosts or prokaryotic organisms partially account for these genes. However, giant viral genomes also contain genes that are unique to viruses, the origin of which is hotly debated (*6*, *12*, *13*). Do these genes originate in vertical gene transfer from a very old viral common ancestor? The small number of genes shared among modern viruses argues against this possibility. Viral genome mosaicism is also suggested by the occurrence of very similar genes in different viruses (*14*). Furthermore, a substantial amount of horizontal gene transfer may occur between viruses. The Sputnik virophage now provides a new potential vehicle for such horizontal gene transfers. In fact, the Sputnik genome encodes several genes that may originate in vastly different viruses.

Assessing the proportions of vertical gene transfer and virus-virus horizontal gene transfer now appears crucial for understanding the evolution of giant viruses, refining the concept of virus lineage, and elucidating gene flow in the virosphere. The unusual features of the giant Mimivirus revived the popular, yet unresolved question: "Are viruses alive?" The discovery that some of them can get sick adds a new twist to this old debate.

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10.1126/science.1164839

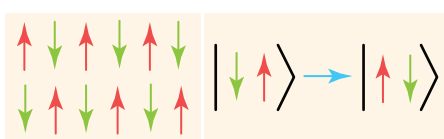
PHYSICS

An End to the Drought of Quantum Spin Liquids

Patrick A. Lee

After decades of searching, several promising examples of a new quantum state of matter have now emerged.

Electrons possess magnetic behavior through the quantum mechanical property of spin. The magnetic properties of materials then arise from the collective interaction of electrons on atoms within the crystal. Below a transition temperature, the electron spins of normal magnets "freeze" into an ordered array of magnetic dipoles. Whether the ordering is ferromagnetic (all the dipoles point in the same direction) or antiferromagnetic (the dipoles on adjacent sites point in opposite directions) is determined by the sign and strength of the interaction between the electrons. Early theoretical work has indicated a departure from these ordered states, suggesting that quantum mechanical fluctuations of the spin could be so strong that ordering would be suppressed and the spin ensemble would remain in a liquid-like state, even down to the lowest temperatures. Experimental evidence, which has until recently remained elusive, is emerging in favor of this long-predicted state of quantum matter.



Ordered spins. (**Left**) Néel's picture of antiferromagnet ordering with an alternate spin-up–spin-down pattern across the lattice. (**Right**) Quantum fluctuations lead to mutual spin flips, which Landau argued would disorder Néel's state.

To understand the controversy surrounding this exotic quantum spin liquid state, it is instructive to go back to the description of antiferromagnetism. Soon after the invention of quantum mechanics, Heisenberg pointed out that electron spins on neighboring atoms can have short-range interaction due to quantum mechanical exchange. Louis Néel

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