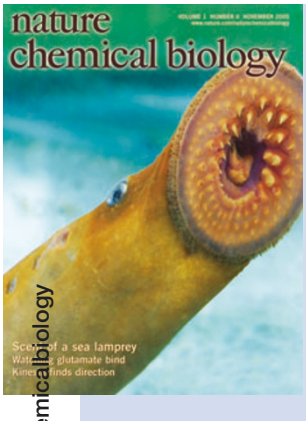
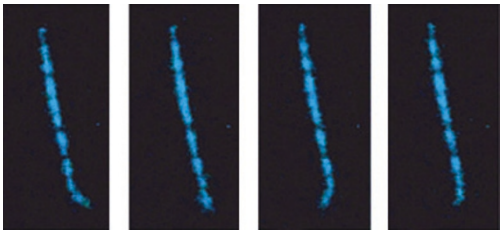
IN THIS ISSUE



COVER STORY

The sea lamprey *(Petromyzon marinus)* is an ancient parasitic fish that survives by sucking the bodily juices out of larger fish. After invading the Great Lakes of North America in the early 20th century, it devastated the regional fishing industry by preying on commercially important fish species. Researchers have searched for small molecules involved in the mating and migratory habits of the sea lamprey in order to apply these molecules as potential control agents for these parasitic organisms. After a 15-year search, Sorensen, Hoye and coworkers report the identification and structural characterization of a mixture of steroid-like compounds that are secreted by lamprey larvae and attract adult fish to suitable spawning areas. By concentrating thousands of liters of water containing the larvae, the team identified three compounds that direct the swimming of adult sea lampreys. Using chemical synthesis and NMR spectroscopy, the team showed that the three compounds contain a steroid scaffold but are modified with sulfate and unusual amino groups. Under appropriate conditions, the pheromone mixture is a potent signal to direct the migrating adult sea lampreys. The identification of this class of sea lamprey pheromones provides new chemical inspiration for ways to manage the ecological problem created by the invading sea lamprey. **[Letters, p. 324; News & Views, p. 316]** *TLS*

Kinesin takes a walk



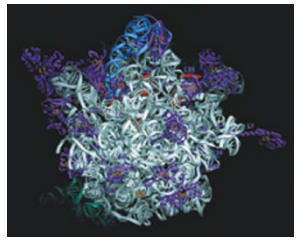
Kinesin is a molecular motor protein that moves one step at a time along microtubules in a manner similar to walking. Using this forward motion, kinesin transports vesicles around cells. Although many details about the mechanism of kinesin motion are known, there are still important questions remaining about what makes kinesin choose its direction and what forces are involved in propelling kinesin along. Yanagida and colleagues find that it is entropy, rather than enthalpy, that favors forward over backward movement. To account for this entropic difference, the authors propose a model in which a forward step is a better steric fit than a backward step. Yajima and Cross followed kinesin moving along microtubules fitted with a side arm. By watching the side arm, they identified a rotational motion that accompanies forward steps. Both of these papers clarify the mechanism of kinesin motion and open up new questions into the precise molecular contacts involved in kinesin walking. [Letters, p. 338; Articles, p. 342; News & Views, p. 319] *JK*

In This Issue written by Mirella Bucci, Joanne Kotz and Terry L. Sheppard

Glutamate in action

Glutamate is a neurotransmitter in the central nervous system, and it has important roles in learning and memory. Although there is detailed structural information about the glutamate receptor in the free and glutamate-bound conformations, there is little information about the mechanism of glutamate binding. In this issue, Jayaraman and colleagues use submillisecond time-resolved FTIR, combined with a caged analog of glutamate, to visualize the glutamate binding pathway. On the basis of vibrational spectroscopy, the authors propose a model that involves an initial step in which glutamate docks into the receptor through interactions with the glutamate α-carboxylate moiety, followed by a receptor cleft closure mediated primarily by interactions with the γ-carboxylate of glutamate. **[Letters, p. 329; News & Views, p. 317]** *JK*

Chemical probes for RNA and beyond



Yusupov *et al*/Science 2001

Small molecules have the potential to serve as unique links between chemical, structural and cellular biology. RNA and ribosome structures, the mechanisms of ribozyme-catalyzed reactions and the functions of individual kinases have all been elucidated by way of discriminating chemical probes. A commentary by Doudna discusses how classical as well as novel chemical tricks can lead to new discoveries into some of the most interesting catalytic proteins and RNAs. With their origins in classical chemistry, small molecules, acting alone or derivatized at the business end of enzymatic catalysts, provide a scaffold to build foundational knowledge and to answer outstanding questions spanning various disciplines. [Commentary, p. 300] *MB*

HCV kicked off the raft

The liver-damaging RNA virus hepatitis C (HCV) tends to become resistant to agents that target viral enzymes. In the search for new drug targets, Sakamoto and coworkers screened a natural product library in a recently developed HCV replicon cell culture system. They found that the lipophilic compound NA255 showed remarkable inhibition of HCV replication. In investigating the compound's mode of action, the authors found that NA255 blocked cellular *de novo* sphingolipid biosynthesis by inhibiting serine palmitoyltransferase, the rate-limiting enzyme in sphingolipid biosynthesis. HCV replication factors, such as RNA-dependent RNA polymerase, bind to the components of Golgi lipid rafts. These results demonstrate that host sphingolipids are required to support HCV replication at the lipid rafts. By targeting host machinery, this approach may minimize the ability of the virus to develop resistance. **[Letters, p. 333]** *MB*