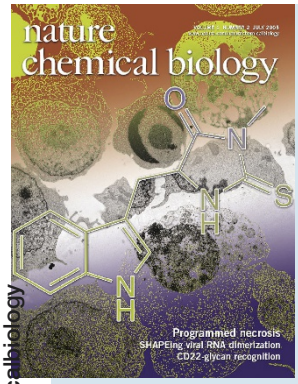
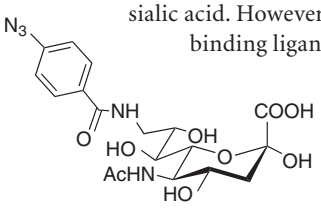



## COVER STORY

There are two major forms of cell death, apoptosis and necrosis. In apoptosis, a specific set of molecular pathways leads to cellular death, whereas necrosis is generally believed to be a passive response to cellular damage. Using high-throughput screening, Yuan and colleagues identified a chemical inhibitor of death receptor–induced necrotic cell death, necrostatin-1. The observed specificity of necrostatin-1 for blocking necrotic cell death and not apoptosis provides evidence that, much like apoptosis, necrosis can also be triggered by precise cellular pathways. In further investigating this pathway, which the authors named necroptosis, they found that it has an important role in a mouse model of ischemic brain injury. Thus, necrostatin-1 is a promising probe for necroptosis and a therapeutic lead for treating stroke. [**Articles, p. 112; News & Views, p. 68**] *JK*

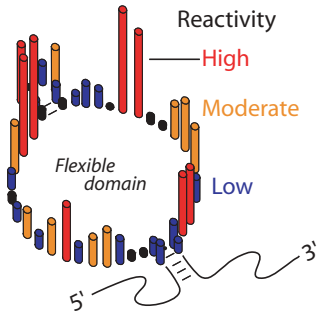
## Trapping glycoprotein interactions

Uncovering interactions between proteins and glycans on the surface of cells is difficult, as traditional biochemical approaches disrupt the cell-surface environment. The function of CD22, an immunoregulator, is modulated by binding to other B-cell glycoproteins, a process mediated by glycans terminating in sialic acid. However, the identity of these CD22 *cis*-binding ligands has been unclear. Paulson and coworkers describe the incorporation of a photoactive sialic acid analog into B-cell surface glycoproteins using the cell's own biosynthetic machinery. On photoactivation, protein-glycan cross-linking occurs, leaving CD22 covalently attached to its binding partner. Analysis of the high-molecular-weight CD22 complex did not reveal molecules previously thought to be CD22 ligands. Instead, the authors' results suggest that CD22 is modulated by CD22 homomultimerization. [**Letters, p. 93; News & Views, p. 69**] *GW*




## Viral RNA dimerization

Retroviruses contain two molecules of RNA that are packaged together to form the infectious viral particle. The RNAs are linked together by noncovalent interactions to form an RNA dimer, which is known to be important for retroviral infectivity. To better understand dimerization, Weeks and colleagues first used a competition assay to accurately determine the region of RNA necessary for dimer formation. The authors then used a chemical approach to probe the structure of this minimal dimerization domain, taking advantage of a chemical that selectively reacts with, and covalently labels, nucleotides that are not involved in base-pairing interactions. With this method, the authors found a region in the monomeric form of the dimerization domain that is highly flexible. By eliminating the need for an existing set of base-pairing interactions to be broken before dimerization, this conformationally flexible region may reduce the energetic costs associated with dimer formation. [**Articles, p. 104; News & Views, p. 67**] *JK*




## Reacting to histamine

G protein–coupled receptors (GPCRs) are critical transducers of extracellular signals to intracellular responses. Although a number of conformational changes are known to occur in response to agonist stimulation, the molecular mechanism connecting agonist binding to downstream structural rearrangements has not been clear. Leurs and colleagues used a combination of computational modeling and biochemical experiments to investigate the changes induced by histamine binding to the histamine $H_1$ receptor. They proposed an activation pathway in which histamine binding causes serine 3.36 to change rotamer conformation, from which they mapped a pathway to subsequent conformational changes. [**Letters, p. 98**] *JK*

## TRP sensation

TRP channels are $Ca^{2+}$-permeable ion channels involved in sensory perceptions, from taste to tactile sensations and vision. These channels respond to a diverse array of stimuli including temperature, chemicals and mechanical force. Even an individual channel can be gated by multiple mechanisms, for instance capsaicin and heat, or menthol and cold. In their review, Voets and colleagues discuss the biological roles of these receptors and how they function. [**Review Articles, p. 85**] *JK*

## Molecular libraries galore

Diversity-oriented synthesis (DOS) methods focus on the synthesis of large collections of small molecules to enable the study of biological systems and to advance drug discovery efforts. Combined with high-throughput screening, DOS allows the simultaneous searching of small-molecule space and biological target space. In his review, Tan discusses how small-molecule libraries are designed and synthesized and provides several case studies showing how DOS libraries have been used to expand synthetic chemistry and our understanding of biology. [**Review Articles, p. 74**] *TLS*

*In This Issue written by Greg Watt, Joanne Kotz and Terry L. Sheppard.*