
## Focus on molecular metrics

The length of a cellular or organismal component enables its functional specialization. For instance, the variation in the chain lengths of very long-chain fatty acids determines whether they are involved in membrane processes such as curvature or in signaling systems [**Research Highlights, p. 611**]. Being able to count generations of cell populations [**Elements, p. 603**] or levels of nutrients [**News & Views, p. 607**], or being able to reliably generate trimers as with a *Streptomyces coelicolor* siderophore synthetase [**Letter, p. 652**], is also critical for time- and space-keeping measurements. This issue features articles that examine how chemical and biological systems make measurements and regulate their own space and time. The length of chromosome ends (telomeres) is directly related to the age of an organism. Blasco reviews research that implicates telomerase, the telomere maintenance enzyme, as being critically important in the aging process and in stem cell renewal and its evil sister, cancer [**Review, p. 640**]. How length is dictated is also the focus of a Perspective by Iovine, who examines the similarities among genetic mechanisms that regulate length in zebrafish fins, fly wings and vertebrate limbs [**Perspective, p. 613**]. Lu reviews how the timing of various cellular processes can be dictated by the rate of proline isomerization [**Review, p. 619**]. The ability of cells and tissues to dictate their own spatial interaction with their external environment is also at the center of circadian signaling systems, which respond at a biochemical level to daily and seasonal changes in light. Kay reviews circadian signaling as a cycle that can be manipulated therapeutically [**Review, p. 630**]. We also report on a long-standing circadian rhythm mystery in plants [**Research Highlights, p. 611**]. Biological systems measure time in many different increments, and Buonomano comments on the ability of biological systems to dictate time differently across scales that span many orders of magnitude [**Commentary, p. 594**]. Because of the periodicity of action potentials, neurons and neural networks in particular specialize in timing, and this is now becoming better understood [**Research Highlights, p. 611**]. Horological methods, as described by Miyawaki [**Commentary, p. 598**], should help scientists determine the spatiotemporal regulation of biological events more directly. *MB*

## Fully synthetic

**Cancer cells often overexpress cell surface sugars, and vaccines directed against these carbohydrates are an attractive strategy for treating cancer. However, the low immunogenicity of carbohydrates has made it difficult to induce high antibody titers to these epitopes. Ingale *et al.* have now synthesized a 'three-component' vaccine that links a tumor-associated carbohydrate epitope and a T-helper epitope with a Toll-like receptor agonist that functions as an adjuvant—a molecule that increases the immune response. When injected into mice, the combination of the three vaccine components in a single chemical species elicited very high titers of IgG antibodies that recognized cancer cells expressing the carbohydrate epitope. [Letters p. 663; News & Views, p. 605]** *JK*

## Morpholinos in a flash

The usefulness of morpholinos—antisense oligonucleotides that are widely used for gene knockdown in zebrafish—is limited by their constitutive expression. To achieve spatial and temporal resolution, Shestopalov *et al.* designed morpholinos that are 'caged' through a photocleavable linker. Because zebrafish are transparent, these modified morpholinos could be activated by light at a specific time or in a specific region of the zebrafish. This method for conditional gene silencing will open up new opportunities for investigating gene function in this vertebrate model organism. [**Brief Communication, p. 650**] *JK*

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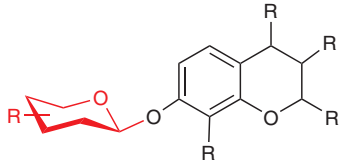
## Sugar transfer




**Sugars appended to natural products are often critical for biological activity, but they can present a significant synthetic challenge. Although biosynthesis using glycosyltransferases is a potential alternative, many natural-product glycosyltransferases accept a very limited range of substrates, and efforts to engineer increased substrate tolerance have been largely unsuccessful. By developing a high-throughput fluorescence-based activity assay, Williams *et al.* used directed evolution to create more promiscuous glycosyltransferase variants. The resulting enzymes could use a broader range of both donor sugars and acceptor substrates, which should make them important tools for glycosylating small molecules. [Letter, p. 657; News & Views, p. 604]** *JK*

## Cathepsins unquenched

The cysteine cathepsin proteases have emerged as promising targets for both the diagnosis and treatment of cancer. As a result, methods to monitor cathepsin activity *in vivo* can provide important therapeutic information. Quenched activity-based probes are substrate mimics that produce a fluorescent signal only after covalently reacting with the targeted enzyme. Blum *et al.* have developed quenched, near-infrared fluorescent probes that can be used to image cysteine cathepsin activity in tumors in living mice. *In vivo* imaging can be directly followed by *in vitro* biochemical analysis of the covalent modification. This activity-based method can also be used to investigate the *in vivo* effects of inhibitors, thus making these probes important tools for testing potential drug leads. [**Article, p. 668**] *JK*