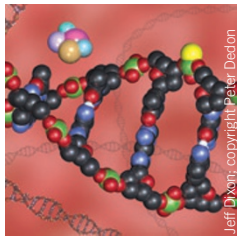

## New pathways for NO signaling

Nitric oxide (NO) generally exerts its signaling effects by activating soluble guanylate cyclase, the enzyme responsible for the synthesis of guanosine 3',5'-cyclic monophosphate (cGMP). However, it is difficult to imagine how signaling specificity is obtained, given the number of downstream pathways regulated by NO production. Experiments by Sawa *et al.* now demonstrate that NO production results in the accumulation of 8-nitro-cGMP within cells. Given its chemical similarity to cGMP, 8-nitro-cGMP effectively mimics cGMP by activating several canonical cGMP signaling pathways. However, the electrophilic and redox properties of 8-nitro-cGMP enable it to engage other pathways, including reacting with cysteine residues to form S-guanylated proteins—a previously unreported protein modification. These discoveries provide new insights into NO physiology and pathology and raise many mechanistic questions about the chemical biology of this newly revealed signaling nucleotide. [**Articles, p. 727; News & Views, p. 687**] *TLS*

## KSP resistance goodbye

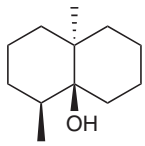
Because of its role in the formation of bipolar mitotic spindles, inhibition of the mitotic kinesin KSP is a promising strategy for anticancer treatment. The well-studied and therapeutically important quinazolinones monastrol and ispinesib function by binding to the loop L5 region of KSP, and cells that have acquired resistance to these inhibitors have mutations in this loop. Luo *et al.* now report that two new selective biaryl KSP inhibitors can act on ispinesib-resistant forms of KSP. The compounds are competitive with ATP, but they act allosterically versus the spindle microtubules by binding to a region distinct from loop L5 and the ATP and microtubule binding sites. The new inhibitors are therefore effective against both wild-type KSP and loop L5 KSP mutants and could prove useful in combination therapy with the quinazolinones. [**Letters, p. 722**] *MB*

## Sulfur cuts in




Though many RNA transcripts undergo post-transcriptional modifications on their way to becoming functional RNAs, covalent modifications to DNA are relatively rare and confined to nucleotide bases. Now, Wang *et al.* report that certain bacterial DNA sequences, including those of *Streptomyces lividans*, contain phosphorothioate modifications. Enzymatic DNA digestion led to dinucleotide fragments that were resistant to nuclease treatment, which suggested that sulfur was incorporated in one of the nonbridging oxygens of the internucleotidyl linkage. Independent chemical synthesis showed that the sulfur occupied the $R_p$ position of this linkage. Although the mechanism of biosynthetic thiolation of DNA and the biological role of this modification remain to be determined, the current study establishes a new postreplicative covalent DNA modification in living systems. [**Brief Communications, p. 709; News & Views, p. 689**] *TLS*

## Digging into geosmin biosynthesis




**The smell of moist soil comes from the microbial metabolite geosmin, whose name means 'earth odor'. Despite the identification of its chemical structure in 1965, the mechanistic details of geosmin biosynthesis have remained elusive. Jiang *et al.* now demonstrate that the N-terminal domain of germacradienol-geosmin synthase catalyzes the cyclization of farnesyl diphosphate to the intermediate germacradienol, and the C-terminal domain of the enzyme, which was previously thought to be inactive, catalyzes the subsequent formation of geosmin. Both of these transformations were found to require $Mg^{2+}$. Since $Mg^{2+}$ is often required for binding substrate diphosphate moieties, its requirement for the first reaction was expected; however, the role of $Mg^{2+}$ in the second reaction is not clear—thus opening up yet new mechanistic questions. [Letters, p. 711; News & Views, p. 690]** *JK*

## Glycoactivation in plants

*Arabidopsis thaliana* is an ideal organism for genetic screening and may prove useful for predicting drug sensitivities in higher organisms. Using chemical screens, Zhao *et al.* found a number of compounds that have strain-specific effects. In particular, the Columbia strain of *A. thaliana* was resistant to the hypocotyl development inhibitor hypostatin, whereas the Landsberg erecta strain was not. Genetic analysis showed that the gene encoding HYR1 is responsible for conferring resistance to hypostatin. HYR1 contains a UDP-glycosyltransferase domain but has no known substrates. Here, the authors found that HYR1 can glycosylate hypostatin and other propiophenone-like xenobiotics, thereby activating the compounds. These results suggest a general drug-sensitivity mechanism and demonstrate the use of *A. thaliana* to identify drug sensitivity alleles. [**Articles, p. 716**] *MB*

## Tag, you're it!

**The ability to label proteins *in vivo* with relatively small tags provides important handles for subsequent investigations into the corresponding biological systems, but attaching these labels in an efficient and selective manner is not always straightforward. Similarly, methods that are orthogonal to known techniques are particularly important to allow introduction of multiple labels for the study of complex biological processes. Popp *et al.* now fully explore the use of sortase-mediated transpeptidation, or 'sortagging', as a versatile orthogonal labeling method for the chemical biology toolbox. This technique, demonstrated here in complex biological mixtures and on live cells to introduce a variety of readily available peptidic tags, only requires the addition of five residues to a protein of interest to allow subsequent sortagging—thus causing minimal disruption to the system. [Brief Communications, p. 707]** *CG*

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