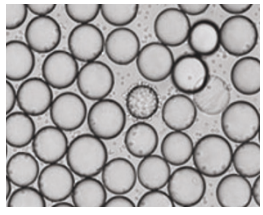

## COVER STORY

The guanine base, which has the lowest ionization potential of any DNA constituent, is particularly susceptible to oxidative damage. Extensive investigations have suggested that DNA damage by one-electron oxidants is concentrated at guanine residues situated at the 5′ end of a string of guanines. This sequence-dependent effect has been attributed to the migration of electron holes to these sites of lowest ionization potential. A new study by Dedon and co-workers challenges this prevailing model of guanine oxidation. The authors performed a systematic investigation of the DNA sequence dependence of oxidation by nitrosoperoxycarbonate, a one-electron oxidant generated in the inflammatory response, and compared their results with those for oxidation induced by riboflavin. Although riboflavin photooxidation followed the standard model, guanine oxidation by nitrosoperoxycarbonate was maximal at guanine residues at G-C sites of the highest ionization potential. Though the mechanistic basis for these differences remains unclear, the study suggests that processes other than DNA charge migration may account for the observed oxidative DNA damage profiles within living cells. **[Brief Communications, p. 365; News & Views, p. 348]** *TLS*

## A sticky copper handshake

Copper atoms are essential cofactors in the respirative reduction of oxygen. In cells, copper is trafficked by metallochaperone proteins and ATP-powered pumps. Bertini and colleagues show that copper is not merely transferred between proteins—it acts as a temporary adhesive. Using NMR spectroscopy and site-directed mutation to study the interaction between the chaperone Atx1 and the P-type ATPase Ccc2, they show that copper is tricoordinated between three key cysteine residues. Even though the surfaces of Atx1 and Ccc2 are electrostatically complementary, copper is necessary for the transient association that, in the cell, shuttles the metal atom from cytosol to membrane. **[Brief Communications, p. 367; News & Views, p. 352]** *KM*

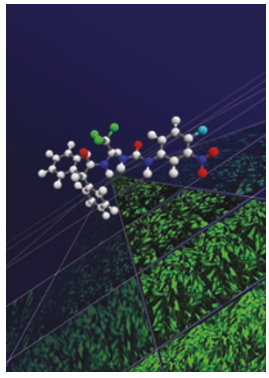
## A stable peptide probe for tumors



**The integrin $\alpha_4\beta_1$ is a heterodimeric transmembrane receptor that aids in the metastasis of tumor cells by binding to fibronectin and strengthening adhesive connections. Peng, Lam and colleagues have used a one-bead-one-compound library strategy to identify peptide ligands based on the $\alpha_4\beta_1$-binding sequence of fibronectin. This strategy allowed for a diverse peptide pool that contained L- as well as D-amino acids, the latter proving to be highly stable and promising for therapeutic use. One of the D-peptides isolated in their screen, LLP2A, binds to the surface of leukemia cells expressing $\alpha_4\beta_1$. Fluorescently labeled LLP2A that was injected into mice with tumor xenografts labeled $\alpha_4\beta_1$-expressing tumors but not normal cells, even those expressing $\alpha_4\beta_1$. The specificity of LLP2A for $\alpha_4\beta_1$-positive tumors and its remarkable stability make it an ideal candidate for therapeutic use. [Articles, p. 381; News & Views, p. 351]** *MB*

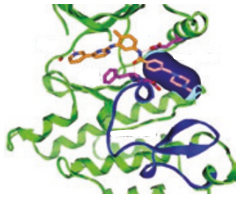
*In This Issue written by Mirella Bucci, Catherine Goodman, Kaspar Mossman and Terry L. Sheppard*

## Bypassing senescence



It is inevitable that as cells age, they either die or become 'replicatively senescent', a state in which the cell remains alive but stops dividing. Uncapped telomeres can cause senescence because they are recognized by the DNA damage machinery as DNA breaks. By screening 20,000 synthetic molecules, Won, Kim and colleagues identified CGK733, a molecule that inhibits senescence in cells with uncapped telomeres. CGK733 also reversibly extends the lifespan of cultured cells by about 20 doublings. Using magnetism-based interaction capture technology, the authors identified the kinases ATM and ATR, which are involved in regulating lifespan, as targets for CGK733. The authors suggest that it is the inhibition of both kinases together that causes the senescence withdrawal seen with CGK733. **[Letters, p. 369]** *MB*

## Teaming up against kinases



**The importance of kinases in maintaining normal cellular function has stimulated intense interest in kinase inhibitor design. Type I inhibitors mimic nucleotide structure to target kinase ATP-binding domains with potent affinities. However, the strong homology of these binding sites limits selectivity. Type II inhibitors primarily bind near the ATP-binding site in an allosteric pocket formed by a conformational shift of the activation loop. The residues of this pocket are less conserved, allowing distinction among proteins. In a Perspective in this issue, Liu and Gray discuss the design and utility of second-generation type II inhibitors that combine type I nucleotide mimicry with discriminating type II motifs. Such inhibitors have the potential for high impact in drug discovery. [Perspective, p. 358]** *CG*

## NO detection? No problem

Although nitric oxide (NO) is an important cellular component, efforts to quantify the spatial and temporal aspects of its behavior have been largely unsuccessful. Previous attempts to monitor NO have relied on secondary methods of detection or have used techniques limited by poor resolution. Lippard and co-workers have now developed a sensitive and selective fluorescent probe that detects NO directly and immediately. When NO is absent, the fluorescein ligand binds Cu(II), resulting in fluorescence quenching. The chelated Cu(II) is then concomitantly reduced and expelled by reaction with NO, generating an enhanced fluorescent signal. The authors used the probe to image NO production in neuroblastomas and macrophages in real time. **[Articles, p. 375; News & Views, p. 349]** *CG*