RESEARCH HIGHLIGHTS
2 Our choices from the recent literature

NEWS AND VIEWS
4 Metabolism: Digging up enzyme functions
Matthew J Wargo ▶ Article p42
5 WNT acylation: Seeing is believing
Luc G Berthiaume ▶ Article p61
7 Immunology: Glyco-engineering ‘super-self’
Matthew S Macauley & James C Paulson ▶ Article p69

REVIEW
9 The role of iron and reactive oxygen species in cell death
Scott J Dixon & Brent R Stockwell
Iron is essential for biological systems but can also damage or kill cells, leading to a variety of disease states. A review of mechanisms leading to Fe- and ROS-dependent cell death highlights the vast array of open questions in this complex field.

BRIEF COMMUNICATION
18 Dynamic ligand binding dictates partial agonism at a G protein-coupled receptor
A Bock, B Chirinda, F Krebs, R Messerer, J Bätz, M Muth, C Dallanoce, D Klingenthal, C Tränkle, C Hoffmann, M De Amici, U Holzgrabe, E Kostenis & K Mohr
Partial agonists are generally thought to promote GPCR conformations that signal suboptimally. Analysis of bifunctional muscarinic M2 receptor ligands now shows that partial agonism can also be predictably defined by a single ligand binding two receptor populations in different orientations.
ARTICLES

21 The multiple antibiotic resistance regulator MarR is a copper sensor in *Escherichia coli*
Z Hao, H Lou, R Zhu, J Zhu, D Zhang, B S Zhao, S Zeng, X Chen, J Chan, C He & P R Chen

Drugs and antibiotics induce oxidation and mobilization of membrane-bound copper(i) ions to copper(ii) species within the *E. coli* cytosol, causing oxidation of a single cysteine residue of the multiple antibiotic-resistance regulator MarR that leads to formation of disulfide-bonded MarR tetramers and release of dimers from sites of transcriptional activity.

29 Chemical inhibition of prometastatic lysyl-tRNA synthetase–laminin receptor interaction

Beyond its canonical role in translation, lysyl-tRNA synthetase (KRS) stabilizes the prometastatic 67-kDa laminin receptor (67LR) in the plasma membrane. A small-molecule inhibitor of the KRS-67LR interaction modulates the KRS-promoted metastatic potential of 67LR without disrupting the normal function of each protein.

35 Imperfect coordination chemistry facilitates metal ion release in the Psa permease
R M Couñago, M P Ween, S L Begg, M Bajaj, J Zuegg, M L O’Mara, M A Cooper, A G McEwan, J C Paton, B Kobe & C A McDevitt

The PsaA binding protein delivers Mn²⁺ to the human pathogen *Streptomyces pneumoniae*. Structural and biochemical studies now explain its metal specificity, showing that metal binding induces a closed complex that is reversible for the desired substrate but irreversible for the inhibitor Zn²⁺.

42 Revealing the hidden functional diversity of an enzyme family

Enzyme annotations often suffer from incomplete functional information for homologous sequences. Extrapolation from one characterized enzyme to multiple possible substrate-enzyme pairs, using bioinformatics and experimental approaches, leads to four distinct β-keto acid cleavage enzyme functional motifs and assignment of 14 new activities.

▶ N&V p4
50  Direct evidence for a covalent ene adduct intermediate in NAD(P)H-dependent enzymes
R G Rosenthal, M-O Ebert, P Kiefer, D M Peter, J A Vorholt & T J Erb

NAD(P)H-dependent enzymes are generally assumed to use a one-step hydride transfer mechanism owing to a lack of evidence for alternative proposals. Spectrophotometric and NMR data now call this assumption into question, defining a covalent substrate cofactor species that is catalytically competent in three unrelated enzymes.

56  A widespread self-cleaving ribozyme class is revealed by bioinformatics
A Roth, Z Weinberg, A G Y Chen, P B Kim, T D Ames & R R Breaker

To date, five classes of naturally occurring self-cleaving ribozymes have been reported. The bioinformatic discovery in bacteria and eukaryotes of twister RNAs, a new ribozyme class that contains a double pseudoknot fold, adds to the list of catalytic RNAs that have roles in cells.

61  Single-cell imaging of Wnt palmitoylation by the acyltransferase porcupine
X Gao & R N Hannoush

Clickable fatty acids coupled with in situ proximity ligation allow visualization of Wnt as it trafficks through the secretory pathway, defining roles for palmitoylation and glycosylation in controlling Wnt activity and exploring the substrate specificity and regulation of the Wnt-modifying porcupine.

69  Glycocalyx engineering reveals a Siglec-based mechanism for NK cell immunoevasion
J E Hudak, S M Canham & C R Bertozzi

Defined phospholipid-functionalized glycopolymers serve as a new tool to identify the mechanistic connection between hypersialylation and immunoprotection, where hypersialylation of tumor cells subverts the immunosurveillance mechanism of NK cells by recruiting the lectin Siglec-7 to inhibit human NK cell activation.

76  PITPs as targets for selectively interfering with phosphoinositide signaling in cells

Phosphatidylinositol transfer proteins (PITPs) are important mediators of phosphoinositide signaling within cells. A small-molecule inhibitor of the PITP Sec14, identified by chemical screening and structure-based design, affects transit through the trans-Golgi network and endosomal system.