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452 Targeted protein degradation: You can glue it too!
Michal J Walczak, Georg Petzold & Nicolas H Thomä  ► Article p514
453 Microbiology: A new language for small talk
Yi-Ming Shi & Helge B Bode  ► Article p551

REVIEW ARTICLE
455 The chemical basis for electrical signaling
William A Catterall, Goragot Wisedchaisri & Ning Zheng
A highlight of the knowledge derived in large part from structural work on physical motions and chemical interactions involved in voltage sensing, pore opening, ion conductance and selectivity, and voltage-dependent inactivation mechanisms of the voltage-gated channels Na, and Ca,

BRIEF COMMUNICATIONS
464 A fully automated flow-based approach for accelerated peptide synthesis
An automated method for solid-phase polypeptide synthesis capitalizes on rapid amide bond formation to enable the production of multiple traditionally difficult-to-synthesize sequences with both high yield and high purity.

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DRUG DISCOVERY
Figuring out coupling
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467 Decoding cyclase-dependent assembly of hapalindole and fischerindole alkaloids
S Li, A N Lowell, S A Newmister, F Yu, R M Williams & D H Sherman

Characterization of a family of Stigonematales (Stig) cyclases that catalyze stereoselective intramolecular C–C bond formation reveals the enzymatic origins of the complex stereochemical patterns in hapalindole and fischerindole alkaloids.

ARTICLES

470 A new genome-mining tool redefines the lasso peptide biosynthetic landscape

RODEO, an algorithm developed for RiPP natural product discovery, was applied to map out the gene clusters that encode and tailor lasso peptides and led to the identification and characterization of several new lasso peptide topologies.

479 The Arabidopsis O-fucosyltransferase SPINDLY activates nuclear growth repressor DELLA
R Zentella, N Sui, B Barnhill, W-P Hsieh, J Hu, J Shabanowitz, M Boyce, N E Olszewski, P Zhou, D F Hunt & T-p Sun

Mass spectroscopy analysis combined with in vitro assays reveals that SPINDLY is an O-fucosyltransferase that modifies the growth repressor DELLA and consequently its activity to regulate transcription of target genes.

486 Capzimin is a potent and specific inhibitor of proteasome isopeptidase Rpn11

Two screening approaches converge on capzimin, a first-in-class inhibitor of the Rpn11 protease component of the 19S proteasome. Capzimin stabilizes polyubiquitinated substrates, induces the unfolded protein response, and blocks proliferation of cancer cells.

494 L-2-Hydroxyglutarate production arises from noncanonical enzyme function at acidic pH
A M Intlekofer, B Wang, H Liu, H Shah, C Carmona-Fontaine, A S Rustenbourg, S Salah, M R Gunner, J D Chodera, J R Cross & C B Thompson

Acidification enhances lactate dehydrogenase– and malate dehydrogenase–mediated promiscuous production of l-2-hydroxyglutarate (l-2HG) from α-ketoglutarate and stabilizes HIF-1α levels.
501  Total RNA-seq to identify pharmacological effects on specific stages of mRNA synthesis
S A Boswell, A Snavely, H M Landry, L S Churchman, J M Gray & M Springer

The application of strand-specific total RNA sequencing combined with metagene analysis enables detection of small-molecule-mediated effects on transcription initiation, elongation or RNA processing, and reveals that isoginkgetin blocks transcriptional elongation.

508  The structure of a nucleolytic ribozyme that employs a catalytic metal ion
Y Liu, T J Wilson & D M J Lilley

The structure of the TS (formerly twister sister) ribozyme reveals details about its catalytic mechanism of nucleolytic self-cleavage using a hydrated magnesium ion, and illustrates key differences between it and the related twister ribozyme.

514  Structural basis of PROTAC cooperative recognition for selective protein degradation

The description of the crystal structure of the Brd4 PROTAC compound MZ1 in complex with the human E3 ubiquitin ligase VHL and the Brd4 bromodomain shines new light onto how PROTACs work and enables design of degraders with increased selectivity for Brd4.

522  The Rrp4–exosome complex recruits and channels substrate RNA by a unique mechanism
M A Cvetkovic, J P Wurm, M J Audin, S Schütz & R Sprangers

A methyl-TROSY NMR approach provides a detailed model for how the archaeal exosome cap recruits multiple RNA substrates and channels them one by one into the catalytic barrel for degradation.

529  In silico design of novel probes for the atypical opioid receptor MRGPRX2
K Lansu, J Karpia, J Liu, X-P Huang, J D McCorvy, W K Kroeze, T Che, H Nagase, F I Carroll, J Jin, B K Shoichet & B L Roth

High-throughput screening identifies opioid compounds and prodynorphin-derived peptide agonists of the G protein-coupled receptor MRGPRX2 and informs a homology model that is used for in silico screening to find a small-molecule probe that provokes degranulation in mast cells, which express this receptor.
537 Metagenomic discovery of polybrominated diphenyl ether biosynthesis by marine sponges

Metagenomic analysis and functional characterization of biosynthetic genes uncovers the basis for widespread polybrominated diphenyl ether biosynthesis in cyanobacterial endosymbionts of marine Dysideidae sponges.

544 The direct role of selenocysteine in [NiFeSe] hydrogenase maturation and catalysis
M C Marques, C Tapia, O Gutiérrez-Sanz, A R Ramos, K L Keller, J D Wall, A L De Lacey, P M Matias & I A C Pereira

Structural and functional characterization of a [NiFeSe] hydrogenase and its conversion to the [NiFe] type by mutagenesis indicate roles for the selenocysteine residue in metal incorporation, catalysis, and protection against oxidative deactivation.

551 A Vibrio cholerae autoinducer-receptor pair that controls biofilm formation
K Papenfort, J E Silpe, K R Schramma, J-P Cong, M R Seyedsayamdost & B L Bassler

A new autoinducer-receptor pair, 3,5-dimethylpyrazin-2-ol (DPO)-VqmA, acts in parallel to canonical Vibrio cholerae quorum-sensing pathways. Downstream of VqmA is the small RNA target VqmR, which, like DPO, represses genes required for biofilm formation and toxin production.

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