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REVIEW ARTICLE
879 Force probing of individual molecules inside the living cell is now a reality
Lene B Oddershede
An overview of single-molecule manipulation techniques that overcome the unique challenges related to working in vivo and of the single-molecule force probings realized inside living cells.
BRIEF COMMUNICATION

887 Enzyme redesign guided by cancer-derived IDH1 mutations
Z J Reitman, B D Choi, I Spasojevic, D D Bigner, J H Sampson & H Yan

A new approach for rational enzyme design uses gain-of-function cancer mutations to guide homologous mutations in homoisocitrate dehydrogenase, yielding a biocatalytic path to (R)-2-hydroxyadipate, a precursor for the major commodity chemical adipic acid.

ARTICLES

890 A selective inhibitor of EZH2 blocks H3K27 methylation and kills mutant lymphoma cells

EZH2 is a protein methyltransferase component of the polycomb repressive complex 2 (PRC2) that installs the H3K27me3 chromatin mark. EPZ005687 inhibits EZH2 function and H3K27 trimethylation in cells and selectively kills lymphoma cells that require EZH2 for proliferation.

897 The orphan nuclear receptor Nur77 regulates LKB1 localization and activates AMPK
Y Zhan, Y Chen, Q Zhang, J Zhuang, M Tian, H Chen, L Zhang, H Zhang, J He, W Wang, R Wu, Y Wang, C Shi, K Yang, A Li, Y Xin, T Y Li, J Y Yang, Z Zheng, C Yu, S-C Lin, C Chang, P Huang, T Lin & Q Wu

A small molecule that disrupts interaction between Nur77 and LKB1 leads to LKB1 exit from the nucleus to activate cytoplasmic AMPK and, ultimately, reduces blood glucose and insulin in diabetic mice.

905 Systems-pharmacology dissection of a drug synergy in imatinib-resistant CML
G E Winter, U Rix, S M Carlson, K V Gleixner, F Grebien, M Gridling, A C Müller, F P Breitwieser, M Bilban, J Colinge, P Valent, K L Bennett, F M White & G Superti-Furga

A systems-pharmacology approach reveals that the combined off-target activity of two kinase inhibitors that impedes MAPK signaling to decrease expression of Myc target genes increases apoptosis in CML cells containing gatekeeper mutations in BCR-ABL.
Discovery and biological characterization of geranylated RNA in bacteria
C E Dumelin, Y Chen, A M Leconte, Y G Chen & D R Liu

Mass spectrometric profiling has revealed S-geranylation as a new tRNA modification and identified SelU as the tailoring enzyme in bacterial cells. Nucleotide S-geranylation was found in the anticodon of several tRNAs and regulates translational frameshifting and codon usage.

Discovery of an allosteric mechanism for the regulation of HCV NS3 protein function

A compound derived from a structure-based screen binds to an allosteric site that includes residues of both the helicase and protease domains of HCV NS3, stabilizing an inactive conformation and inhibiting viral replication.

A RubisCO-like protein links SAM metabolism with isoprenoid biosynthesis

Combined omics techniques lead to the functional assignment of four enzymes involved in a new methionine salvage pathway linking polyamine metabolism with isoprenoid biosynthesis. This reaction sequence involves a homolog of nature’s most abundant protein, the CO₂-fixing enzyme RubisCO.

An enzyme-trap approach allows isolation of intermediates in cobalamin biosynthesis
E Deery, S Schroeder, A D Lawrence, S L Taylor, A Seyedarabi, J Waterman, K S Wilson, D Brown, M A Geeyes, M J Howard, R W Pickersgill & M J Warren

The use of abbreviated pathway constructs leads to trapping of a series of cobalamin intermediates, allowing assignment of the full biosynthetic pathway and defining the roles of CobL as a dual-function methyltransferase and CobE as a likely carrier protein, perhaps facilitating metabolic channeling.

The catalytic center of ferritin regulates iron storage via Fe(II)-Fe(III) displacement
K H Ebrahimi, E Bill, P-L Hagedoorn & W R Hagen

Ferritin controls iron concentrations by storing Fe(III), but the mechanism by which Fe(II) is bound and trafficked into the protein core after oxidation remains controversial. Spectroscopic methods in combination with labeling and competition assays now define a mechanism conserved from archaea to humans.