COVER IMAGE
The development of model organisms such as zebrafish and worms progresses from a single cell to the formation of defined tissues and organs. A collection of Commentary, Perspective and Review articles in this issue describe new advances in exploiting the intersection between developmental processes and chemical biology.

The cover image depicts the fate mapping of cellular lineages using different fluorescent dyes in a zebrafish embryo (top, colored in red), a Caenorhabditis elegans embryo (middle, colored in brown) and a mouse embryo (bottom, colored in green) at four distinct stages. The stem cells isolated from the mouse blastocyst are cultured and differentiated into neurons.

Cover art by Erin Dewalt.

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**ARTICLES**

616 Chemical screening identifies ATM as a target for alleviating senescence  
H T Kang, J T Park, K Choi, Y Kim, H J C Choi, C W Jung, Y-S Lee & S C Park  
Ataxia telangiectasia mutated (ATM) directly interacts with and phosphorylates the V-ATPase V1 subunit ATP6V1G1, thereby decreasing V1-V0 assembly in the V-ATPase. Attenuation of ATM activity results in lysosomal pH acidification, recovery of autophagy and alleviation of senescence.

624 Diabetes reversal by inhibition of the low-molecular-weight tyrosine phosphatase  
The generation of low-molecular-weight protein tyrosine phosphatase (LMPTP) knockout mice combined with the identification of a small-molecule LMPTP uncompetitive inhibitor reveals a role for LMPTP in regulating insulin resistance.

**BRIEF COMMUNICATIONS**

607 CRISPR-Cas9 strategy for activation of silent *Streptomyces* biosynthetic gene clusters  
M M Zhang, F T Wong, Y Wang, S Luo, Y H Lim, E Heng, W L Yeo, R E Cobb, B Enghiad, E L Ang & H Zhao  
Most microbial biosynthetic gene clusters are inactive under laboratory culture conditions. A CRISPR-Cas9 genome-editing approach in *Streptomyces* species enables the targeted activation of silent gene clusters and production of encoded natural products.

610 Structural and functional insight into human O-GlcNAcase  
C Roth, S Chan, W A Offen, G R Hemsworth, L I Willems, D T King, V Varghese, R Britton, D J Vocadlo & G J Davies  
Crystal structures of human O-GlcNAc hydrolase (hOGA) fragments show that hOGA’s dimeric structure is organized by swapping of an α-helical element and reveal features of inhibitor binding to the catalytic domain.

613 Insights into activity and inhibition from the crystal structure of human O-GlcNAcase  
Crystallographic analysis of human O-GlcNAc hydrolase (hOGA) fragments containing the catalytic domain, including structures in complex with known inhibitors, suggests that OGA is functional as a dimer and defines opportunities for structure-based drug design.
633  Near-infrared optogenetic pair for protein regulation and spectral multiplexing
T A Redchuk, E S Omelina, K G Chernov & V V Verkhusha

The engineering of Q-PAS1, a single-domain variant of PpsR2, led to an optimized optogenetic system based on the Q-PAS1-BphP1 interaction, which was applied to the regulation of transcription, epigenetic state and protein localization by near-infrared light.

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640  AtaT blocks translation initiation by N-acetylation of the initiator tRNA^{Met}
D Jurėnas, S Chatterjee, A Konijnenberg, F Sobott, L Droogmans, A Garcia-Pino & L Van Melderen

Characterization of an enterohaemorrhagic E. coli toxin-antitoxin system reveals that the toxin AtaT specifically acetylates Met-tRNA^{Met} at the methionyl amine, making it incompetent for translation initiation, which inhibits translation.

647  Phosphorylated glycosphingolipids essential for cholesterol mobilization in Caenorhabditis elegans
S Boland, U Schmidt, V Zagorij, J L Sampaio, R F Fritsche, R Czerwonka, T Lübken, J Reimann, S Penkov, H-J Knölker & T V Kurzchalia

mmPEGC-ZZ is a nonsterol glycolipid involved in early Caenorhabditis elegans larval development that can rescue the growth-arrest phenotype due to sterol deficiency and is controlled by TGF-β to help mobilize internal sterol pools.

655  Mechanistic insights into energy conservation by flavin-based electron bifurcation

Structural analysis and spectroscopy elucidate how pairs of electrons are bifurcated in a flavoenzyme by generating an unstable flavin semiquinone, thus coupling exergonic and endergonic oxidation-reduction reactions.

660  Using the pimeloyl-CoA synthetase adenylation fold to synthesize fatty acid thioesters
M Wang, L Moynié, P J Harrison, V Kelly, A Piper, J H Naismith & D J Campopiano

Structures of pimeloyl-CoA synthetase (BioW) provide insights into its catalytic mechanism and how it selects the correct length of dicarboxylic acid substrate, guiding engineering to make the enzyme capable of producing alternative CoA products.
668 The pimeloyl-CoA synthetase BioW defines a new fold for adenylate-forming enzymes
P Estrada, M Manandhar, S-H Dong, J Deveryshetty, V Agarwal, J E Cronan & S K Nair

Structural analysis of pimeloyl-CoA synthetase (BioW) provides insight into how the enzyme ensures proper substrate positioning and how a key residue ensures proofreading of the reaction through hydrolysis of noncognate adenylated substrates.

675 Selective degradation of splicing factor CAPERα by anticancer sulfonamides

A series of sulfonamides induced the ubiquitin-mediated degradation of the U2AF-related splicing factor, coactivator of activating protein-1 and estrogen receptor α (CAPERα), by promoting direct binding between CAPERα and the CRL4 substrate receptor DCAF15.

681 Global survey of the immunomodulatory potential of common drugs

A high-content screening platform that measures the immunological potential of small-molecule and biologic drugs by computationally determining changes in the physical interactions among peripheral mononuclear leukocytes revealed known immunomodulators and also approved drugs as regulators of unexpected targets, including MST1R.

CORRECTIONS
691 Errata and corrigenda