EDITORIAL

605 Microbiota meet big data

RESEARCH HIGHLIGHTS

606 Our choices from the recent literature

NEWS AND VIEWS

608 Drug selectivity: Running in the family
Marcel Muelbaier & Gerard Drewes ▶ Article p656

609 Allostery: A GPCR’s back door
Klaus Mohr & Evi Kostenis ▶ Brief Communication p629

611 Natural products: Sponge symbionts play defense
Emily P Balskus ▶ Article p648

REVIEW ARTICLE

613 Small-molecule modulation of Ras signaling
Jochen Spiegel, Philipp M Cromm, Gunther Zimmermann, Tom N Grossmann & Herbert Waldmann

There has been a strong effort to devise strategies to interfere with oncogenic Ras for cancer treatment. A review of recent advances in the development of small-molecule inhibitors that impair either Ras localization or protein interactions provides new optimism in this field.

BRIEF COMMUNICATIONS

623 DNA sequencing and CRISPR-Cas9 gene editing for target validation in mammalian cells
Y Smurnyy, M Cai, H Wu, E McWhinnie, J A Tallarico, Y Yang & Y Feng

Drug resistance mutations provide a classical means to identify biological targets of small molecules. A combination of next-generation DNA sequencing with CRISPR-Cas9 genome editing confirms the targets of 6-thioguanine and triptolide and offers a general approach for target identification in cells.
**626** DrugTargetSeqR: a genomics- and CRISPR-Cas9–based method to analyze drug targets  
C Kasap, O Elemento & T M Kapoor

Finding the biological targets of small molecules remains an important challenge in chemical biology and drug discovery. A method involving high-throughput sequencing, mutational analysis and clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 genome editing identifies the targets and potential modes of compound resistance for two anticancer agents.

**629** A potentiator of orthosteric ligand activity at GLP-1R acts via covalent modification  
W M Nolte, J-P Fortin, B D Stevens, G E Aspnes, D A Griffith, L R Hoth, R B Ruggeri, A M Mathiowitz, C Limberakis, D Hepworth & P A Carpino

BETP, a positive allosteric modulator of GLP-1R, a class B GPCR and an important therapeutic target for type II diabetes, covalently modifies two cysteine residues at the receptor’s cytoplasmic face, where one of these enhances agonist-induced signaling.

▶ N&S p609

[In the version of the Table of Contents initially published, the labels for the BETP conditions were swapped in graphical abstract of the Nolte et al. article. The error has been corrected in the HTML and PDF versions of the Table of Contents.]

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**ARTICLES**

**632** Notch inhibition allows oncogene-independent generation of iPS cells  

The addition of a Notch signaling inhibitor to both mouse and human keratinocytes bypasses the use of oncogenes and p53 to increase transcription factor mediated–pluripotent stem cell reprogramming through blocking p21 expression.

**640** Biosynthesis of polybrominated aromatic organic compounds by marine bacteria  
V Agarwal, A A El Gamal, K Yamanaka, D Poth, R D Kersten, M Schorn, E E Allen & B S Moore

Halogenases discovered from biosynthetic clusters that make chlorinated products are known and can make brominated compounds in vitro. Genetic and biochemical data now define the first true 'brominase', a halogenase that cannot use chlorine, which uses an unusual decarboxylative mechanism.

**648** Calyculin biogenesis from a pyrophosphate protoxin produced by a sponge symbiont  
T Wakimoto, Y Egami, Y Nakashima, Y Wakimoto, T Mori, T Awakawa, T Ito, H Kenmoku, Y Asakawa, J Piel & I Abe

Some toxic natural products are made in deactivated forms to avoid damage to the host. Metagenomic mining of sponge symbions and biochemical characterization now define a new inactivating mechanism in which calyculin is made as a pyrophosphate by symbiotic bacteria and cleaved to the active monophosphate by the sponge.

▶ N&S p611
A high-throughput, multiplexed assay for superfamily-wide profiling of enzyme activity

D A Bachovchin, L W Koblan, W Wu, Y Liu, Y Li, P Zhao, I Woznica, Y Shu, J H Lai, S E Poplawski, C P Kiritsy, S E Healey, M DiMare, D G Sanford, R S Munford, W W Bachovchin & T R Golub

The development of a new screening method called EnPlex allows rapid profiling of small molecules against an extensive selection of the serine hydrolase enzyme family, resulting in the identification of both off-targets and potential lead compounds.

Extended ubiquitin species are protein-based DUB inhibitors

D Krutauz, N Reis, M A Nakasone, P Siman, D Zhang, D S Kirkpatrick, S P Gygi, A Brik, D Fushman & M H Glickman

C-terminal extended ubiquitin species, which have been associated with neurodegenerative disorders, were thought to inhibit proteasomes resulting in reduced protein clearance. Biochemical studies now provide evidence that these ubiquitin variants primarily block the activity of the deubiquitinating enzymes.

Rational design of a ligand-based antagonist of jasmonate perception

I Monte, M Hamberg, A Chini, S Gimenez-Ibanez, G García-Casado, A Porzel, F Pazos, M Boter & R Solano

(+)-7-iso-jasmonoyl-l-isoleucine (JA-Ile) is a plant hormone involved in plant development and stress response that signals through a COI1-JAZ co-receptor complex. Structure-guided design led to the identification of a coronatine derivative that antagonizes the COI1-JAZ interaction and blocks jasmonate signaling in plants.

Autophagy induction enhances TDP43 turnover and survival in neuronal ALS models

S J Barmada, A Serio, A Arjun, B Bilican, A Daub, D M Ando, A Tsvetkov, M Pleiss, X Li, D Peisach, C Shaw, S Chandran & S Finkbeiner

Inclusions containing TDP43 are linked to pathologies in several neurodegenerative diseases such as ALS and FTD. Pathogenic TDP43 mutations are now found to shorten the protein’s half-life in individual neurons. Stimulating autophagy with inhibitors improves TDP43 clearance and localization.

A G-quadruplex-containing RNA activates fluorescence in a GFP-like fluorophore

H Huang, N B Suslov, N-S Li, S A Shelke, M E Evans, Y Koldobskaya, P A Rice & J A Piccirilli

Spinach is an RNA aptamer analog of GFP that is widely used for fluorescent labeling of cellular RNAs. Crystal structures of Spinach-fluorophore complexes uncover an unusual G-quadruplex RNA fold that is involved in ligand recognition and tuning of Spinach fluorescence properties.

CORRECTIONS

Errata and Corrigenda