**RESEARCH HIGHLIGHTS**

756  Our choices from the recent literature

**NEWS AND VIEWS**

758  Carbohydrates: Cracking the glycan sequence code
Christopher J Jones & Cynthia K Larive  ▶ Article p827

759  Ion channels: Manipulating the munchies in mice
Myles H Akabas

761  Plant biology: Blocking galactolipid biosynthesis
Kent D Chapman  ▶ Article p834

**BRIEF COMMUNICATIONS**

763  Metabolomics annotates ABHD3 as a physiologic regulator of medium-chain phospholipids
J Z Long, J S Cisar, D Milliken, S Niessen, C Wang, S A Trauger, G Siuzdak & B F Cravatt

An untargeted metabolomics approach identifies C14 phosphatidylcholines (PCs) as specific cellular medium-chain substrates of the lipase ABHD3, as well as C5–C8 short-chain PCs including oxidized pro-atherosclerotic and pro-apoptotic PC phospholipids.

766  Structural basis for cytokinin recognition by Arabidopsis thaliana histidine kinase 4
M Hothorn, T Dabi & J Chory

Histidine kinase 4 from Arabidopsis thaliana (AHK4) is a membrane-bound receptor for cytokinins, a class of plant hormones involved in growth, development and defense. Crystal structures of the AHK4 sensor domain in complex with various natural and synthetic cytokinins reveal important features of ligand recognition by this cytokinin receptor.

**COVER IMAGE**

An in silico high-throughput screen of the dopamine D3 receptor based on a homology model prior to publication of the crystal structure and a subsequent virtual screen based on the crystal structure of the receptor after it became available both identified new ligands with verified activities. The image is a rendition of the homology model of the G protein-coupled receptor, plus seven new ligands from the homology model screen. Cover art by Erin Dewalt, based on an image from Ryan Coleman.

Article, p769

**ON THE COVER**

CHEMICAL PROBES
Galvanizing plant lipids
Article p834; News & Views p761

DRUG RESISTANCE
A Notch in PI3K’s arsenal
Article p787

PEPTIDES
Genome mining 2.0
Article p794

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**ARTICLES**

769  **Ligand discovery from a dopamine D₃ receptor homology model and crystal structure**
J Carlsson, R G Coleman, V Setola, J J Irwin, H Fan, A Schlessinger, A Sali, B L Roth & B K Shoichet

A virtual screen of the GPCR D3R based on a homology model prior to publication of the crystal structure and a subsequent virtual screen based on the crystal structure of the receptor once it became available both identified new ligands with verified activities.

779  **RF1 knockout allows ribosomal incorporation of unnatural amino acids at multiple sites**

Nonsense suppression, or reassigning stop codons to encode for other amino acids, offers a method for expanding the genetic code of proteins. Deletion of release factor 1 in an *Escherichia coli* strain enables the incorporation of non-natural amino acids into proteins at multiple sites.

787  **A chemical-genetic screen reveals a mechanism of resistance to PI3K inhibitors in cancer**

A chemical-genetic study predicts mechanisms of resistance to PI3K inhibitors. Activation of NOTCH signaling, which leads to c-MYC expression, can overcome cancer cell dependency on PI3K signaling for growth. NOTCH and PI3K have not previously been linked in breast cancer.

794  **A mass spectrometry–guided genome mining approach for natural product peptidogenomics**
R D Kersten, Y-L Yang, Y Xu, P Cimermancic, S-J Nam, W Fenical, M A Fischbach, B S Moore & P C Dorrestein

Peptidic natural products are theoretically amenable to characterization by mass spectrometry, but proteomics programs are not trained to discover these compounds. A new strategy uses mass spectrometry and bioinformatics iteratively to rapidly identify both ribosomal and nonribosomal sequences, yielding multiple new compounds.

803  **(R)-Profens are substrate-selective inhibitors of endocannabinoid oxygenation by COX-2**

Rapid reversible inhibitors of the oxygenation activity of COX-2, including ibuprofen and naproxen, selectively inhibit the enzyme with endocannabinoid 2-AG substrates but not with arachidonic acid, and this substrate-selective inhibition may be important for the analgesic activity of the drugs.
810 On-resin N-methylation of cyclic peptides for discovery of orally bioavailable scaffolds
A single trimethylated species is obtained in an on-resin N-methylation reaction of a cyclic hexapeptide. This regioselectivity is driven by conformation and the presence of intramolecular hydrogen bonds and is correlated with membrane permeability of the peptides.

818 Affinity-based proteomics reveal cancer-specific networks coordinated by Hsp90

827 The proteoglycan bikunin has a defined sequence
M Ly, F E Leach III, T N Laremore, T Toida, I J Amster & R J Linhardt
Complex polysaccharides are generally thought not to have a defined carbohydrate sequence because their synthesis is not template-directed. Detailed mass spectrometry of bikunin now counters this dogma, showing that each molecular weight species consists of only a single sequence.

834 Chemical inhibitors of monogalactosyldiacylglycerol synthases in Arabidopsis thaliana
C Y Botté, M Deligny, A Roccia, A-L Bonneau, N Sai’dani, H Hardré, S Acï, Y Yamaryo-Botté, J Jouhet, E Dubots, K Loizeau, O Bastien, L Bréhélin, J Joyard, J-C Cintrat, D Falconet, M A Block, B Rousseau, R Lopez & E Maréchal
Mono- and digalactosyldiacylglycerols (MGDGs and DGDGs) are glycolipids that are central to plant metabolism and photosynthetic membrane biogenesis. Galvestine-1, a small molecule inhibitor of MGDG synthases in Arabidopsis thaliana, reveals a new role for these galactolipids in pollen-tube development.

843 Discovery of parallel pathways of kanamycin biosynthesis allows antibiotic manipulation
J W Park, S R Park, K K Nepal, A R Han, Y H Ban, Y J Yoo, E J Kim, E M Kim, D Kim, J K Sohng & Y J Yoon
Investigations into kanamycin biosynthesis and identification of new pathway intermediates surprisingly point to the substrate specificity of two glycosyltransferases as controlling flux into parallel pathways, allowing changes to product profiles and structures by varying these gatekeeper enzymes.

CORRECTIONS

853 Corrigenda