EDITORIAL
1 The art of the revision

RESEARCH HIGHLIGHTS
2 Our choices from the recent literature

NEWS AND VIEWS
4 Drug discovery: New Btk inhibitor holds promise
   Rudi W Hendriks
   ▶ Article p41

5 Structural biology: The twist in Crk signaling revealed
   Linda K Nicholson & Soumya De
   ▶ Article p51

7 Systems biology: Metabolites do social networking
   Douglas B Kell

REVIEW ARTICLE
9 Chemical modulators of autophagy as biological probes and potential therapeutics
   Angeleen Fleming, Takeshi Noda, Tamotsu Yoshimori & David C Rubinsztein

Autophagy has emerged as a drug target for various diseases including cancer and neurodegeneration. Small molecules that affect components of the autophagic machinery and signaling pathways have led to new insights into autophagic mechanisms and also serve as lead compounds for therapeutic application.

ON THE COVER
Protease inhibitors
   Sticking it to HCV
   Brief Communication p22

Signaling proteins
   An SH3 toggle switch
   Article p51; News & Views p5

Plants
   Finishing phenylalanine
   Brief Communication p19

COVER IMAGE
In inflamed arthritis tissue, activated B cells and macrophages contribute to joint inflammation, cartilage destruction and bone loss. Specific Btk inhibition, explored by a new chemical probe, CGI1746, has the potential to interrupt the BCR and FcgR signaling pathways in these cells and ameliorate arthritis. The montage by Karin Reif with images from Ziprasidon, a painting by the artist Klari Reis (www.klarireis.com), depicts activated B cells and macrophages in synovial tissue.

Cover art by Erin Dewalt.
Article, p41
**Brief Communications**

19  Prephenate aminotransferase directs plant phenylalanine biosynthesis via arogenate  
H Maeda, H Yoo & N Dudareva

In addition to its incorporation into proteins, phenylalanine serves as an important precursor for natural products and components of the plant cell wall. The identification of the last gene in phenylalanine biosynthesis explains why flux in this pathway traffics through an arogenate intermediate in plants.

22  Selective irreversible inhibition of a protease by targeting a noncatalytic cysteine  

A potent hepatitis C virus protease protein inhibitor forms an irreversible covalent bond to a virally conserved noncatalytic cysteine in the protease substrate-binding pocket identified in a bioinformatic analysis.

**Articles**

25  Cardiac glycosides are potent inhibitors of interferon-β gene expression  
J Ye, S Chen & T Maniatis

Cardiac glycosides, which target the Na⁺-K⁺-ATPase, block IFNβ expression by increasing intracellular Na⁺ levels to inhibit the ATPase activity of the RNA sensor RIG-I, affecting the signaling cascade downstream.

34  Signaling diversity of PKA achieved via a Ca²⁺-cAMP-PKA oscillatory circuit  
Q Ni, A Ganesan, N-N Aye-Han, X Gao, M D Allen, A Levchenko & J Zhang

PKA initiates and modulates the frequency of oscillations of Ca²⁺ and cAMP in insulin-secreting cells and itself oscillates to provide spatiotemporal control of downstream signals on the basis of diverse inputs.
41 Specific Btk inhibition suppresses B cell- and myeloid cell-mediated arthritis

Binding of the small-molecule inhibitor CGI1746 to Bruton’s tyrosine kinase (Btk), a therapeutic target for rheumatoid arthritis, induces an inactive Btk conformation. Application of this specific chemical probe reveals two Btk signaling pathways involved in inflammatory arthritis.

▶ N&V p4

51 Structural basis for regulation of the Crk signaling protein by a proline switch
P Sarkar, T Saleh, S-R Tzeng, R B Birge & C G Kalodimos

Structural analysis by NMR reveals that the Gly237-Pro238 bond of the signaling protein Crk in the cis form stabilizes an autoinhibited conformation between two tandem SH3 domains, whereas the trans form promotes an activated conformation for Abl kinase binding.

▶ N&V p5

58 Identification of lysine succinylation as a new post-translational modification
Z Zhang, M Tan, Z Xie, L Dai, Y Chen & Y Zhao

Post-translational modifications are critical to protein structure and function. Mass spectrometry, antibody pulldowns and other lines of evidence now establish the presence of lysine succinylation across numerous proteins and species.

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