

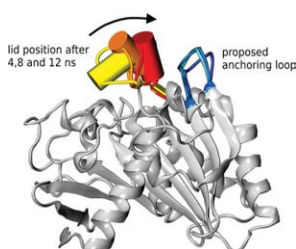
# IN THIS ISSUE



## 2131 **The crystal structure of a bacterial Sufu-like protein defines a novel group of bacterial proteins that are similar to the N-terminal domain of human Sufu**

Debanu Das, Robert D. Finn, Polat Abdubek, Tamara Astakhova, Herbert L. Axelrod, Constantina Bakolitsa, Xiaohui Cai, Dennis Carlton, Connie Chen, Hsiu-Ju Chiu, Michelle Chiu, Thomas Clayton, Marc C. Deller, Lian Duan, Kyle Ellrott, Carol L. Farr, Julie Feuerhelm, Joanna C. Grant, Anna Grzechnik, Gye Won Han, Lukasz Jaroszewski, Kevin K. Jin, Heath E. Klock, Mark W. Knuth, Piotr Kozbial, S. Sri Krishna, Abhinav Kumar, Winnie W. Lam, David Marciano, Mitchell D. Miller, Andrew T. Morse, Edward Nigoghossian, Amanda Nopakun, Linda Okach, Christina Puckett, Ron Reyes, Henry J. Tien, Christine B. Trame, Henry van den Bedem, Dana Weekes, Tiffany Wooten, Qingping Xu, Andrew Yeh, Jiadong Zhou, Keith O. Hodgson, John Wooley, Marc-André Elsliger, Ashley M. Deacon, Adam Godzik, Scott A. Lesley, and Ian A. Wilson

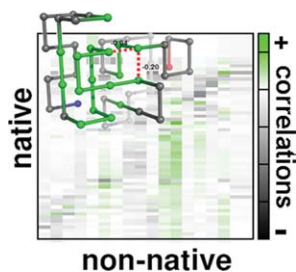
The Sufu (Suppressor of Fused) protein is crucial in Hedgehog signaling that modulates development in higher organisms from flies to humans. No counterpart of this pathway has been identified in bacteria. The crystal structure of NGO1391 from *Neisseria gonorrhoeae* has led to the identification of about 300 bacterial proteins of unknown function from 200 species that are related in structure to the human Sufu. The results have allowed a significant expansion of the Pfam SUFU family of proteins, which should help guide further experiments to investigate the role of these bacterial proteins in cellular function and protein evolution.



## 2122 **Solvent-induced lid opening in lipases: A molecular dynamics study**

Sascha Rehm, Peter Trodler, and Jürgen Pleiss

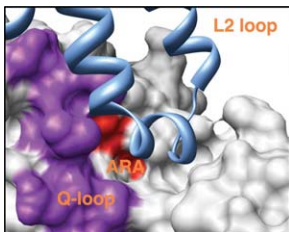
Most lipases cover their substrate binding site with a mobile lid in the inactive state. Upon activation of the lipase by contact with a hydrophobic solvent or at a hydrophobic interface, the lid opens. In this work, the molecular mechanism of this interfacial activation was studied for three lipases from *Candida rugosa* (CRL), *Rhizomucor miehei* (RML), and *Thermomyces lanuginose* (TLL) by multiple molecular dynamics simulations. Both the closed and the open structure of each lipase were simulated in water and in an organic solvent, toluene. The authors present different pathways of the conformational transitions and suggest kinetic bottlenecks in CRL. Additionally, a loop in RML and TLL was proposed to work as an anchor at hydrophobic interfaces.



## 2196 **Non-native interactions play an effective role in protein folding dynamics**

Patrícia F. N. Faísca, Ana Nunes, Rui D. M. Travasso, and Eugene I. Shakhnovich

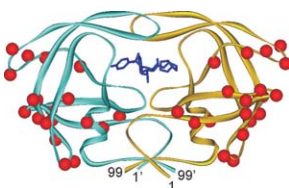
Non-native interactions—interactions between amino acid residues that are not present in the native structure—may be established with significant frequency during protein folding. Analysis of the correlations between native and non-native interactions in extensive computer simulations of simplified protein models strongly supports the idea that non-native interactions play an influential role in the folding process. Indeed, the formation of native interactions may be either hindered or assisted by the non-native interactions, and, quite remarkably, these two opposing effects can be observed until the last stage of the folding process.



## 2110 **Functional hot spots in human ATB-binding cassette transporter nucleotide binding domains**

Libusha Kelly, Hisayo Fukushima, Rachel Karchin, Jason M. Gow, Leslie W. Chinn, Ursula Pieper, Mark R. Segal, Deanna L. Kroetz, and Andrej Sali

The human ABC transporter superfamily contains 48 membrane proteins, mutations in 18 of which are known to be disease-associated. Because it is not feasible to experimentally characterize the functional consequences of the many mutations already identified in ABC transporters, which include the cystic fibrosis protein CFTR and multidrug resistance transporters, the authors here used a combined experimental and computational approach for functional characterization of naturally occurring genetic variation across the human ABC transporter superfamily. Kelly, *et al.* predicted the effects of unannotated non-synonymous single nucleotide polymorphisms in seven ABC transporters and validated three of the predictions experimentally with the multidrug transporter MRP4; experimental results confirmed two predictions. Combining computational and experimental approaches therefore represents an efficient framework for future studies on genetic variation in this superfamily.



## 2055 **Autocatalytic maturation, physical/chemical properties, and crystal structure of group N HIV-1 protease: Relevance to drug resistance**

Jane M. Sayer, Johnson Agniswamy, Irene T. Weber, and John M. Louis

The mature protease of HIV group N (PR1<sub>N</sub>) is distinguished from the predominantly studied group M protease (PR1<sub>M</sub>) by 20 amino acid substitutions in naturally variable regions, some corresponding to minor drug resistance mutations identified in PR1<sub>M</sub>. Despite significant differences between the crystal structures of PR1<sub>N</sub> and PR1<sub>M</sub>, inhibitor binding studies indicate that PR1<sub>N</sub> polymorphisms may not directly confer drug resistance. The PR1<sub>N</sub> precursor undergoes autocatalytic maturation concomitant with the appearance of active dimeric PR1<sub>N</sub>. The drug darunavir promotes dimerization of the precursor monomer and inhibits maturation, although with weaker binding than to mature PR1<sub>N</sub>. Unique solubility and dimerization properties of PR1<sub>N</sub> and its precursor may facilitate their use to study inhibitors of dimerization.