



**Cover image:** Pictured is an artistic illustration of a folded protein on a computer chip. A collection of articles in the From Basic Mechanisms and Cellular Machineries to AI Solutions in Protein Folding Special Feature highlights recent advances in the use of deep learning models and AI algorithms to understand and predict protein structures and folding patterns. Together, the articles explore the physico-chemical rules that govern protein folding, the biological machinery of protein quality control, and the origins of neurodegenerative pathologies associated with protein misfolding. See the Introduction to the Special Feature, e2411135121. Image credit: Art by Sarina Bromberg (Three Arrows Cooperative Society, Putnam Valley, NY), with concept by Charles D. Kocher and Ken A. Dill (Stony Brook University, Stony Brook, NY).

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**THIS WEEK IN PNAS**

This week's research highlights

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**OPINION**

Leading scientists discuss current issues

e2403489121 **Extended time, elevated expectations: The unappreciated downsides of pausing the tenure clock**

Maria Holland, Katharina Maisel, Carolyn B. Ibberson, Laura K. Wiley, David C. Burnett, Emily M. Mace, and Mary Williard Elting

**QNAS**

Interviews with leading scientific researchers and newsmakers

e2413366121 **QnAs with Susan T. Lovett**

Sarah C. P. Williams

**RETROSPECTIVE**

e2411980121 **Diana Wall: A champion for lives underfoot**

John C. Moore, David C. Coleman, Camille T. Dungy, Tony Frank, Kathleen A. Galvin, Peter C. de Ruyter, Diane M. McKnight, Johan Six, and Wim H. van der Putten

**COMMENTARIES**

e2410953121 **A dirigent of the ring for strigolactone stereochemistry**

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Salim Al-Babili

See companion article, e2313683121, in vol. 121, issue 26

e2412543121 **Fully protected Marine Protected Areas do not displace fisheries**

Mark John Costello

See companion article, e2400592121, in vol. 121, issue 29

e2413203121 **Revealing the architecture of the membrane-bound Flotillin cage assembly**

Brett M. Collins

See companion article, e2409334121, in vol. 121, issue 29

**PERSPECTIVE**

e2319077121 **The path to scientifically sound biodiversity valuation in the context of the Global Biodiversity Framework**

Eli P. Fenichel, Monica F. Dean, and Oswald J. Schmitz

**LETTERS**

e2318689121 **Evolution is not driven by and toward increasing information and complexity**

Meredith Root-Bernstein

e2406598121 **Reply to Root-Bernstein: Increasing complexity allows for the pervasiveness of low-complexity entities and is not anthropocentric**

Michael L. Wong, Stuart Bartlett, Carol E. Cleland, Heather Demarest, H. James Cleaves II, Anirudh Prabhu, Jonathan I. Lunine, and Robert M. Hazen

e2411350121 **La Soufrière volcanic eruption in 2021 was not responsible for the high Fe, Al, or Mn concentrations found in stranded *Sargassum* spp.**  
Tristan Gobert, Solène Connan, Benjamin Châtelain, Marie-Laure Rouget, Valérie Stiger-Pouvreau, and Matthieu Waeles

e2412718121 **Reply to Gobert et al.: The need for more research to understand changes in new pelagic sargassum ecosystem during its advection**  
Carla Botelho Machado, Robert Marsh, Jessica K. Hargreaves, Hazel A. Oxenford, Gina-Marie Maddix, Dale F. Webber, Mona Webber, and Thierry Tonon

## INAUGURAL ARTICLE

e2402194121 **A network frame offers a promising transdisciplinary tool for understanding complex health and health care system problems like suicide**  
[OPEN ACCESS](#)  
Bernice A. Pescosolido

## FROM BASIC MECHANISMS AND CELLULAR MACHINERIES TO AI SOLUTIONS IN PROTEIN FOLDING SPECIAL FEATURE

### INTRODUCTION

e2411135121 **Protein folding: From physico-chemical rules and cellular machineries of protein quality control to AI solutions**  
[OPEN ACCESS](#)  
Ulyana Shimanovich and F. Ulrich Hartl

### PERSPECTIVES

e2315002121 **AlphaFold two years on: Validation and impact**  
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Oleg Kovalevskiy, Juan Mateos-Garcia, and Kathryn Tunyasuvunakool

e2315000121 **Origins of life: The Protein Folding Problem all over again?**  
Charles D. Kocher and Ken A. Dill

e2314999121 **Addressing epistasis in the design of protein function**  
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### RESEARCH ARTICLES

e2315005121 **AlphaFold2-based prediction of the co-condensation propensity of proteins**  
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Shengyu Zhang, Christine M. Lim, Martina Occhetta, and Michele Vendruscolo

e2315009121 **Insights into the interaction between UGGT, the gatekeeper of folding in the ER, and its partner, the selenoprotein SEP15**  
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Robert V. Williams, Kevin P. Guay, Owen A. Hurlbut Lesk, Eugenia M. Clerico, Daniel N. Hebert, and Lila M. Gierasch

e2315006121 **Residues 2 to 7 of  $\alpha$ -synuclein regulate amyloid formation via lipid-dependent and lipid-independent pathways**  
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Katherine M. Dewison, Benjamin Rowlinson, Jonathan M. Machin, Joel A. Crossley, Dev Thacker, Martin Wilkinson, Sabine M. Ulamec, G. Nasir Khan, Neil A. Ranson, Patricija van Oosten-Hawle, David J. Brockwell, and Sheena E. Radford

e2315510121 **Sound-mediated nucleation and growth of amyloid fibrils**  
[OPEN ACCESS](#)  
Anna Kozell, Aleksei Solomonov, Roman Gaidarov, Doron Benyamin, Irit Rosenhek-Goldian, Harry Mark Greenblatt, Yaakov Levy, Ariel Amir, Uri Raviv, and Ulyana Shimanovich

e2315007121 **Conservation of kinetic stability, but not the unfolding mechanism, between human transthyretin and a transthyretin-related enzyme**  
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Marcus Jäger, Jeffery W. Kelly, and Martin Gruebele

## BRIEF REPORT

e2407629121 **Are self-reported fertility preferences biased? Evidence from indirect elicitation methods**  
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e2410164121 **DNA-DISK: Automated end-to-end data storage via enzymatic single-nucleotide DNA synthesis and sequencing on digital microfluidics**  
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Julie B. Hipp, Paolo Z. Ramos, Qingsong Liu, Norman J. Wagner, and Jeffrey J. Richards

e2317944121 **Local strain inhomogeneities during electrical triggering of a metal-insulator transition revealed by X-ray microscopy**  
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Pavel Salev, Elliot Kisiel, Dayne Sasaki, Brandon Gunn, Wei He, Mingzhen Feng, Junjie Li, Nobumichi Tamura, Ishwor Poudyal, Zahirul Islam, Yayoi Takamura, Alex Frano, and Ivan K. Schuller

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Jimmy Gonzalez Nuñez, Jayson Paulose, Wolfram Möbius, and Daniel A. Beller

e2405986121 **Capturing RAS oligomerization on a membrane**  
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e2408313121 **Universal cold RNA phase transitions**  
[OPEN ACCESS](#)  
Paolo Rissone, Aurélien Severino, Isabel Pastor, and Felix Ritort

e2312511121 **Genetic mechanisms for impaired synaptic plasticity in schizophrenia revealed by computational modeling**  
Tuomo Mäki-Marttunen, Kim T. Blackwell, Ibrahim Akkouh, Alexey Shadrin, Mathias Valstad, Torbjørn Elvsåshagen, Marja-Leena Linne, Srdjan Djurovic, Gaute T. Einevoll, and Ole A. Andreassen

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- e2404726121 **Internal catalysis significantly promotes the bond exchange of covalently adaptable polyurethane networks**  
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- e2410504121 **Sustainable H<sub>2</sub>O<sub>2</sub> production via solution plasma catalysis**  
Shuang Liang, Qi Wu, Changhua Wang, Rui Wang, Dashuai Li, Yanmei Xing, Dexin Jin, He Ma, Yichun Liu, Peng Zhang, and Xintong Zhang
- e2400267121 **Light-induced H<sub>2</sub> generation in a photosystem I-O<sub>2</sub>-tolerant [FeFe] hydrogenase nanoconstruct**  
Tristen D. Rumbaugh, Michael J. Gorka, Carol S. Baker, John H. Golbeck, and Alexey Silakov

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- e2408226121 **How obliquity has differently shaped Pluto's and Triton's landscapes and climates**  
Tanguy Bertrand, François Forget, and Emmanuel Lellouch
- e2320143121 **Tropical Andean climate variations since the last deglaciation**  
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- e2401638121 **Unexpected increase of the deuterium to hydrogen ratio in the Venus mesosphere**  
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Arnaud Mahieux, Sébastien Viscardy, Roger Vincent Yelle, Hiroki Karyu, Sarah Chamberlain, Séverine Robert, Arianna Piccialli, Loïc Trompet, Justin Tyler Erwin, Soma Ubukata, Hiromu Nakagawa, Shungo Koyama, Romain Maggiolo, Nuno Pereira, Gaël Cessateur, Yannick Willame, and Ann Carine Vandaele

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- e2401874121 **The deflection of fatigued neck**  
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- e2405628121 **Pressure-enhanced sensing of tissue oxygenation via endogenous porphyrin: Implications for dynamic visualization of cancer in surgery**  
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## PHYSICS

- e2401540121 **Uncovering underlying physical principles and driving forces of cell differentiation and reprogramming from single-cell transcriptomics**  
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## SUSTAINABILITY SCIENCE

- e2402970121 **Optimizing restoration: A holistic spatial approach to deliver Nature's Contributions to People with minimal tradeoffs and maximal equity**  
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- e2402267121 **Race adjustments in clinical algorithms can help correct for racial disparities in data quality**  
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- e2322821121 **Vulnerability in research ethics: A call for assessing vulnerability and implementing protections**  
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Michael G. Findley, Faten Ghosn, and Sara J. Lowe

### PSYCHOLOGICAL AND COGNITIVE SCIENCES

- e2308950121 **GPT is an effective tool for multilingual psychological text analysis**  
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Steve Rathje, Dan-Mircea Mirea, Iliia Sucholutsky, Raja Marjeh, Claire E. Robertson, and Jay J. Van Bavel
- e2403609121 **Sexual assault victims face a penalty for adjacent consent**  
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Jillian J. Jordan and Roseanna Sommers
- e2401687121 **The neocortical infrastructure for language involves region-specific patterns of laminar gene expression**  
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Maggie M. K. Wong, Zhiqiang Sha, Lukas Lütje, Xiang-Zhen Kong, Sabrina van Heukelum, Wilma D. J. van de Berg, Laura E. Jonkman, Simon E. Fisher, and Clyde Francks

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- e2402194121 **A network frame offers a promising transdisciplinary tool for understanding complex health and health care system problems like suicide**  
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- e2317725121 **Decline in carbon emission intensity of global agriculture has stagnated recently**  
Zhaohai Bai, Nannan Zhang, Wilfried Winiwarter, Jiafa Luo, Jinfeng Chang, Pete Smith, Stewart Ledgard, Yan Wu, Chaopeng Hong, Giulia Conchedda, and Lin Ma

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- e2317725121 **Decline in carbon emission intensity of global agriculture has stagnated recently**  
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e2407285121 **An artificially evolved gene for herbicide-resistant rice breeding**  
Jin Dong, Xin-He Yu, Jiangqing Dong, Gao-Hua Wang, Xin-Long Wang, Da-Wei Wang, Yao-Chao Yan, Han Xiao, Bao-Qin Ye, Hong-Yan Lin, and Guang-Fu Yang

## BIOCHEMISTRY

e2410164121 **DNA-DISK: Automated end-to-end data storage via enzymatic single-nucleotide DNA synthesis and sequencing on digital microfluidics**  
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e2405986121 **Capturing RAS oligomerization on a membrane**  
Sangho D. Yun, Elena Scott, Jing-Yuan Chang, Hanieh Bahramimoghaddam, Michael Lynn, Carter Lantz, David H. Russell, and Arthur Laganowsky

e2400267121 **Light-induced H<sub>2</sub> generation in a photosystem I-O<sub>2</sub>-tolerant [FeFe] hydrogenase nanoconstruct**  
Tristen D. Rumbaugh, Michael J. Gorka, Carol S. Baker, John H. Golbeck, and Alexey Silakov

e2403392121 **MAVS Cys508 palmitoylation promotes its aggregation on the mitochondrial outer membrane and antiviral innate immunity**  
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Yinong Liu, Dan Hou, Wenzhe Chen, Xuan Lu, Garrison P. Komaniacki, Yilai Xu, Tao Yu, Sophia M. Zhang, Maurine E. Linder, and Hening Lin

e2400912121 **Disorder-to-order active site capping regulates the rate-limiting step of the inositol pathway**  
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Toni K. Träger, Fotis L. Kyrilis, Farzad Hamdi, Christian Tüting, Marie Alfes, Tommy Hofmann, Carla Schmidt, and Panagiotis L. Kastiris

e2315759121 **ATAD5 functions as a regulatory platform for Ub-PCNA deubiquitination**  
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e2405632121 **Light regulates widespread plant alternative polyadenylation through the chloroplast**  
M. Guillermina Kubaczka, Micaela A. Godoy Herz, Wei-Chun Chen, Dinghai Zheng, Ezequiel Petrillo, Bin Tian, and Alberto R. Kornblihtt

## BIOPHYSICS AND COMPUTATIONAL BIOLOGY

e2401540121 **Uncovering underlying physical principles and driving forces of cell differentiation and reprogramming from single-cell transcriptomics**  
Ligang Zhu, Songlin Yang, Kun Zhang, Hong Wang, Xiaona Fang, and Jin Wang

e2408313121 **Universal cold RNA phase transitions**  
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Paolo Rissone, Aurélien Severino, Isabel Pastor, and Felix Ritort

e2321999121 **The importance of the location of the N-terminus in successful protein folding in vivo and in vitro**  
Natalie R. Dall, Carolina A. T. F. Mendonça, Héctor L. Torres Vera, and Susan Marqusee

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e2404738121 **Circadian period is compensated for repressor protein turnover rates in single cells**  
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e2401251121 **IL-13 and IL-17A activate  $\beta$ 1 integrin through an NF- $\kappa$ B/Rho kinase/PIP5K1 $\gamma$  pathway to enhance force transmission in airway smooth muscle**  
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e2408551121 **Contribution of intraflagellar transport to compartmentalization and maintenance of the photoreceptor cell**  
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e2409341121 **An AAGAB-to-CCDC32 handover mechanism controls the assembly of the AP2 adaptor complex**  
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e2405959121 **mTORC1 phosphorylates and stabilizes LST2 to negatively regulate EGFR**  
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## ECOLOGY

e2319487121 **Linking physiology, epidemiology, and demography: Understanding how lianas outcompete trees in a changing world**  
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e2319989121 **Predicting undetected native vascular plant diversity at a global scale**  
Barnabas H. Daru

e2406314121 **Increasing environmental variability inhibits evolutionary rescue in a long-lived vertebrate**  
T. J. Clark-Wolf, P. Dee Boersma, Floriane Plard, Ginger A. Rebstock, and Briana Abrahms

e2322063121 **Persistent species relationships characterize migrating bird communities across stopover sites and seasons**  
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e2411487121 **Range expansions across landscapes with quenched noise**  
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e2405993121 **Elucidating the sustainability of 700 y of Inuvialuit beluga whale hunting in the Mackenzie River Delta, Northwest Territories, Canada**  
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Mikkel Skovrind, Marie Louis, Steven H. Ferguson, Dmitry M. Glazov, Dennis I. Litovka, Lisa Loseto, Ilya G. Meschersky, Mariah M. Miller, Martin Petr, Lianne Postma, Viatcheslav V. Rozhnov, Michael Scott, Michael V. Westbury, Paul Szpak, T. Max Friesen, and Eline D. Lorenzen

## GENETICS

e2401687121 **The neocortical infrastructure for language involves region-specific patterns of laminar gene expression**  
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Maggie M. K. Wong, Zhiqiang Sha, Lukas Lütje, Xiang-Zhen Kong, Sabrina van Heukelum, Wilma D. J. van de Berg, Laura E. Jonkman, Simon E. Fisher, and Clyde Francks

e2403133121 **Polyomavirus ALTOs, but not MTs, downregulate viral early gene expression by activating the NF- $\kappa$ B pathway**  
Nicholas J. H. Salisbury, Supriya Amonkar, Joselyn Landazuri Vinueza, Joseph J. Carter, Ann Roman, and Denise A. Galloway

e2402262121 **Rtt105 stimulates Rad51-ssDNA assembly and orchestrates Rad51 and RPA actions to promote homologous recombination repair**  
Xuejie Wang, Xiacong Zhao, Zhengshi Yu, Tianai Fan, Yunjing Guo, Jianqiang Liang, Yanyan Wang, Jingfei Zhan, Guifang Chen, Chun Zhou, Xinghua Zhang, Xiangpan Li, and Xuefeng Chen

## IMMUNOLOGY AND INFLAMMATION

e2321686121 **Lipidomic scanning of self-lipids identifies headless antigens for natural killer T cells**  
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Tan-Yun Cheng, T. Praveena, Srinath Govindarajan, Catarina F. Almeida, Daniel G. Pellicci, Wellington C. Arkins, Ildiko Van Rhijn, Koen Venken, Dirk Elewaut, Dale I. Godfrey, Jamie Rossjohn, and D. Branch Moody

e2401658121 **Alloreactive memory CD4 T cells promote transplant rejection by engaging DCs to induce innate inflammation and CD8 T cell priming**  
Irene Saha, Amanpreet Singh Chawla, Ana Paula B. N. Oliveira, Eileen E. Elfers, Kathrynne Warrick, Hannah E. Meibers, Viral G. Jain, Thomas Hagan, Jonathan D. Katz, and Chandrashekhar Pasare

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e2405628121 **Pressure-enhanced sensing of tissue oxygenation via endogenous porphyrin: Implications for dynamic visualization of cancer in surgery**  
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Arthur F. Petusseau, Marien Ochoa, Matthew Reed, Marvin M. Doyley, Tayyaba Hasan, Petr Bruza, and Brian W. Pogue

e2402998121 **Single-nuclei sequencing of uterine serous carcinoma reveals racial differences in immune signaling**  
K. Grace Foley, Mazhar Adli, and J. Julie Kim

e2406519121 **Phase separation of PML/RAR $\alpha$  and BRD4 coassembled microspeckles governs transcriptional dysregulation in acute promyelocytic leukemia**  
Yi Zhang, Jiacheng Lou, Yabin Liu, Peng Jin, Yun Tan, Huan Song, Wen Jin, Dan Wang, Fangyi Dong, Shishuang Wu, Hai Fang, Saijuan Chen, Zhu Chen, and Kankan Wang

e2409262121 **Phosphorylation of Insig-2 mediates inhibition of fatty acid synthesis by polyunsaturated fatty acids**  
**OPEN ACCESS**  
Jing Tian, Joseph L. Goldstein, Shili Li, Marc M. Schumacher, and Michael S. Brown

## MICROBIOLOGY

e2400657121 **Microsporidian EnP1 alters host cell H2B monoubiquitination and prevents ferroptosis facilitating microsporidia survival**  
Jingyu Guan, Liyuan Tang, Yongliang Wang, Ming Fu, Tian Xia, Kai Zheng, Musa Makongoro Sabi, Hua Cong, Juncheng Wang, Chunxue Zhou, Huaiyu Zhou, Louis M. Weiss, Hongnan Qu, and Bing Han

e2322938121 **An additional proofreader contributes to DNA replication fidelity in mycobacteria**  
Ming-Zhi Deng, Qingyun Liu, Shu-Jun Cui, Yi-Xin Wang, Guoliang Zhu, Han Fu, Mingyu Gan, Yuan-Yuan Xu, Xia Cai, Sheng Wang, Wei Sha, Guo-Ping Zhao, Sarah M. Fortune, and Liang-Dong Lyu

e2403235121 **Zika virus NS5 protein inhibits type I interferon signaling via CRL3 E3 ubiquitin ligase-mediated degradation of STAT2**  
Wenlin Ren (任文琳), Chonglei Fu (付崇雷), Yu Zhang (张羽), Xiaohui Ju (鞠晓辉), Xi Jiang (姜熙), Jingwei Song (宋晶伟), Mingli Gong (龚明丽), Zhuoyang Li (李卓阳), Wenchun Fan (范文春), Jun Yao (姚骏), and Qiang Ding (丁强)

e2408540121 **Identification of a family of peptidoglycan transpeptidases reveals that *Clostridioides difficile* requires noncanonical cross-links for viability**  
Kevin W. Bollinger, Ute Müh, Karl L. Ocius, Alexis J. Apostolos, Marcos M. Pires, Richard F. Helm, David L. Popham, David S. Weiss, and Craig D. Ellermeier

## NEUROSCIENCE

e2312511121 **Genetic mechanisms for impaired synaptic plasticity in schizophrenia revealed by computational modeling**  
Tuomo Mäki-Marttunen, Kim T. Blackwell, Ibrahim Akkouh, Alexey Shadrin, Mathias Valstad, Torbjørn Elvsåshagen, Marja-Leena Linne, Srdjan Djurovic, Gaute T. Einevoll, and Ole A. Andreassen

e2321659121 **A computational study of how an  $\alpha$ - to  $\gamma$ -motoneurone collateral can mitigate velocity-dependent stretch reflexes during voluntary movement**  
Grace Niyo, Lama I. Almofeez, Andrew Erwin, and Francisco J. Valero-Cuevas

e2411167121 **Entrainment echoes in the cerebellum**  
Benedikt Zoefel, Omid Abbasi, Joachim Gross, and Sonja A. Kotz

e2409343121 **Cortical neurodegeneration caused by *Psen1* mutations is independent of A $\beta$**   
**OPEN ACCESS**  
Kuo Yan, Chen Zhang, Jongkyun Kang, Paola Montenegro, and Jie Shen

e2404454121 **Thirst-driven hygro-sensory suppression promotes water seeking in *Drosophila***  
Li-An Chu, Chu-Yi Tai, and Ann-Shyn Chiang

e2405901121 **Mice lacking *Astn2* have ASD-like behaviors and altered cerebellar circuit properties**  
**OPEN ACCESS**  
Michalina Hanzel, Kayla Fernando, Susan E. Maloney, Zach Horn, Shiao-ching Gong, Kärt Mätlik, Jiajia Zhao, H. Amalia Pasolli, Søren Heissel, Joseph D. Dougherty, Court Hull, and Mary E. Hatten

## PHARMACOLOGY

e2405465121 **Mechanism of gabapentinoid potentiation of opioid effects on cyclic AMP signaling in neuropathic pain**  
Anibal Garza-Carbajal, Alexis Bavencoffe, Juan J. Herrera, Kayla N. Johnson, Edgar T. Walters, and Carmen W. Dessauer

e2320257121 **A PIKfyve modulator combined with an integrated stress response inhibitor to treat lysosomal storage diseases**  
William C. Hou, Lynée A. Massey, Derek Rhoades, Yin Wu, Wen Ren, Chiara Frank, Herman S. Overkleeft, and Jeffrey W. Kelly

## PHYSIOLOGY

e2319724121 **Zfp697 is an RNA-binding protein that regulates skeletal muscle inflammation and remodeling**  
Jorge C. Correia, Paulo R. Jannig, Maya L. Gosztyla, Igor Cervenka, Serge Ducommun, Stine M. Præsthholm, José M. Dias, Kyle D. Dumont, Zhengye Liu, Qishan Liang, Daniel Edsgård, Olof Emanuelsson, Paul Gregorevic, Håkan Westerblad, Tomas Venckunas, Marius Brazaitis, Sigita Kamandulis, Johanna T. Lanner, Ana I. Teixeira, Gene W. Yeo, and Jorge L. Ruas

## PLANT BIOLOGY

e2404199121 **Genetic improvement of phosphate-limited photosynthesis for high yield in rice**  
Bin Ma, You Zhang, Yanfei Fan, Lin Zhang, Xiaoyuan Li, Qi-Qi Zhang, Qingyao Shu, Jirong Huang, Genyun Chen, Qun Li, Qifei Gao, Xin-Guang Zhu, Zuhua He, and Peng Wang

## CORRECTION

### NEUROSCIENCE

e2414866121 **Neural auditory contrast enhancement in humans**  
Anahita H. Mehta, Lei Feng, and Andrew J. Oxenham