**OUTLOOK** Haemophilia

**IMMUNE-CHECKPOINT** 

CANCER

NeGenome & Co. v. Univ. of Chicago

UNIV. CHICAGO EX. 2056

ENERGY

'NIGHT-TIME'

COOLING BY DAY

PGR2019-00002

**BLOCKADE IN** 

> NATURE.COM/NATURE

\$10.00US \$12.99CAN

27 November 2014

THE INTERNATIONAL WEEKLY JOURNAL OF SCIENCE

Antitumour immunity enhanced by inhibiting PD-L1/PD-1 and identifying mutant neo-antigens PAGES 496, 558, 563, 568, 572 & 577

> DO NOT REMOVE FROM CURRENT PERIODICALS ROOM

PEER REVIEW ACCEPT YOUR OWN PAPER How some scientists are

Find authenticated court documents without watermarks at docketalarm.com.

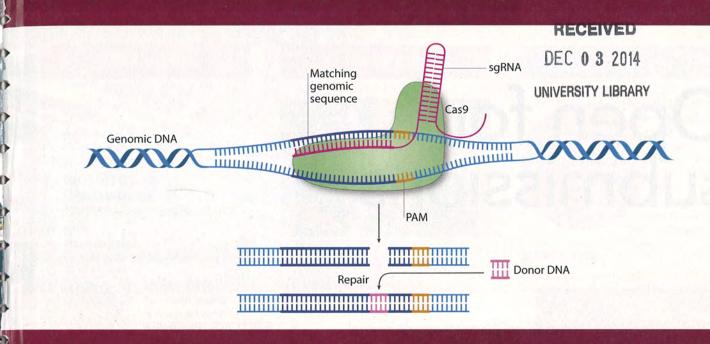
MICROSCOPY

THE CASE FOR

AIMING HIGHER

Atomic resolution is there

**<u>nature</u>** REVIEWS **MICROBIOLOGY** 

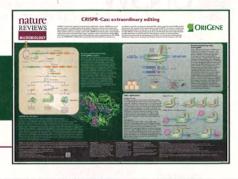


# **FREE POSTER**

# **CRISPR-Cas: extraordinary editing**

The CRISPR–Cas system evolved to provide adaptive immunity in bacteria and archaea against invading genetic elements, such as viruses and plasmids. The mechanism of interference is based on CRISPR RNAs, which are derived from foreign DNA and mediate the detection of invading nucleic acids, followed by degradation by the Cas proteins. This poster presents the molecular mechanism of CRISPR–Cas interference and highlights the use of specifically engineered guide RNAs and the Cas9 nuclease for the editing of virtually any desired genome, in addition to other applications such as imaging in live cells and the regulation of gene expression.

Download the poster at: www.nature.com/nrmicro/posters/crispr



Produced with support from

DICENIE

Find authenticated court documents without watermarks at docketalarm.com.

# CONTENTS

27 November 2014 / Vol 515 / Issue No 7528

# THIS WEEK

### **EDITORIALS**

**465 CLIMATE** Agree to agree

Other nations must follow the lead of the United States and China

**465 INFECTIOUS DISEASE Ebola opportunity** Slowdown should be put to good use

**466 SPACE** Moon on a stick Crowdfunded mission worth a try

### **WORLD VIEW**

467 Open access is tiring out peer reviewers Martijn Arns Scholarly system must adapt to workload

## RESEARCH HIGHLIGHTS

**468 SELECTIONS FROM THE** SCIENTIFIC LITERATURE



Termite queen rules roost / North China earthquake history / Old papers back in vogue / Tagged fish predated / Remote control of epilepsy / Greenland on ice

### SEVEN DAYS

**470 THE NEWS IN BRIEF** 

Oil pipeline rejected / Charity sells royalty rights / Holt to head AAAS / LHC data go open access / Wave-power company enters administration / 'Polar code' to regulate ships

## CAREERS

**597 DIVERSITY** Structural approach Materials scientists are trying to broadon the range of poon!

## NEWS IN FOCUS



- **473 EMISSIONS** US-China deal renews hopes for talks
- **474 MARINE SCIENCE** Data-management issues delay observatory project
- **476 NEUROSCIENCE** FDA considers how to regulate brain-linked devices
- 477 MEDICINE Clampdown on clinical-trial reporting
- **478 PUBLISHING** Open-data dictum not always followed
- **479 ECOLOGY** Galapagos gift-shop closure shortchanges conservation

### FEATURES



PUBLISHING

The peerreview scam Evidence of self-review exposes weaknesses in system PAGE 480

**484 NUCLEAR POWER** Decoorately cooking plutonium

## COMMENT



Hasten high resolution Stephen J Pennycook & Sergei V Kalinin Precision microscopes are needed to analyse atoms effectively

## **BOOKS & ARTS**



**MILITARY SCIENCE** 

# Spoils for science

Ann Finkbeiner reviews two books on the legacies of the cold war PAGE 489

- **490 ORNITHOLOGY Fowl domination** Ewen Callaway
- **491 CLIMATE SCIENCE** A climate trance **Richard Van Noorden**

### CORRESPONDENCE

492 Ebola virus control / Brain training in its infancy / China's progress in research / Philae's marathon achievement





Find authenticated court documents without watermarks at docketalarm.com.

# CONTENTS

27 November 2014 / Vol 515 / Issue No 7528

## RESEARCH

### **NEW ONLINE**

493 Papers published this week at nature.com

### **NEWS & VIEWS**

494 CLIMATE SCIENCE El Niño's variable history

Evolution of the El Niño–Southern Oscillation over the past 21,000 years Josephine R Brown SEE LETTER P.550

**495 MAMMALIAN EVOLUTION** 

A beast of the southern wild A complete skull of a Madagascan gondwanathere Anne Weil SEE ARTICLE P.512

**496 CANCER** 

Antitumour immunity gets a boost Responses to immune-checkpoint blockade in multiple cancers Jedd D Wolchok & Timothy A Chan SEE LETTERS PP.558–581

498 ASTRONOMY Cosmic triangles and black-hole masses Estimating geometric distances to active galactic nuclei and quasars Martin Elvis SEE LETTER P.528

- 499 DEVELOPMENTAL BIOLOGY Polarize to elongate Toll receptors direct cell rearrangement during embryo elongation Ulrich Tepass SEE ARTICLE P.523
- 501 DIET

Food choices for health and planet Projected diets linked to greenhousegas emissions and poor health *Elke Stehfest* **SEE ARTICLE P.518** 

502 IMMUNOLOGY Tolerance lies in the timing Lck-bound co-receptor recruitment is rate-limiting for negative selection Nicholas R J Gascoigne

### REVIEW

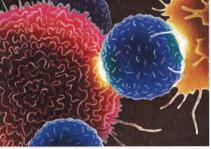
505 ECOLOGY Belowground biodiversity and ecosystem functioning R D Bardgett & W H van der Putten

ARTICLES

512 EVOLUTION First cranial remains of a gondwanatherian mammal reveal

# on the cover Prime cancer targets

A tumour cell (left) interacts with three T cells and a tumour-infiltrating immune cell. This issue features five papers reflecting intense interest in the targeting of immune checkpoints as cancer therapy, and detailed work on identifying patients likely to respond to this therapeutic strategy. PAGES 496, 558, 563, 568, 572 & 571



- 518 NUTRITION Global diets link environmental sustainability and human health D Tilman & M Clark SEE N&V P.501
- 523 DEVELOPMENTAL BIOLOGY A positional Toll receptor code directs convergent extension in Drosophila A C Paré et al. SEE N&V P.499

### LETTERS

- 528 ASTRONOMY A dust-parallax distance of 19 megaparsecs to the supermassive black hole in NGC 4151 S F Hönig, D Watson, M Kishimoto & J Hjorth SEE N&V P.498
- 531 SPACE PHYSICS An impenetrable barrier to ultrarelativistic electrons in the Van Allen radiation belts D N Baker et al.
- 535 MATERIALS SCIENCE Metallization of vanadium dioxide driven by large phonon entropy J D Budai et al.

temperature under direct sunlight A P Raman, M A Anoma, L Zhu, E Rephaeli & S Fan

- 545 MOLECULAR ELECTRONICS Design and fabrication of memory devices based on nanoscale polyoxometalate clusters *C Busche* et al.
- 550 PALAEOCLIMATE Evolution and forcing mechanisms of El Niño over the past 21,000 years Z Liu et al. SEE N&V P.494
- 554 BIOPHYSICS Multiplex single-molecule interaction profiling of DNA-barcoded proteins L Gu et al.
- 558 CANCER MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer *T Powles* et al. SEE N&V P. 496
- 563 CANCER Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients R S Herbst et al. SEE N&V P. 496
- 568 CANCER PD-1 blockade induces responses by inhibiting adaptive immune resistance P C Tumeh et al. SEE N&V P.496
- 572 CANCER Predicting immunogenic tumour mutations by combining mass spectrometry and exome sequencing *M Yadav* et al. SEE N&V P. 496
- 577 CANCER Checkpoint blockade cancer immunotherapy targets tumourspecific mutant antigens *M M Gubin* et al. SEE N&V P. 496
- 582 NEUROSCIENCE Histone H2A.Z subunit exchange controls consolidation of recent and remote memory I B Zovkic et al.
- 587 PLANT SCIENCES Epigenetic reprogramming that prevents transgenerational inheritance of the vernalized state *P* Crevillén et al.
- 591 VIROLOGY A structure-based mechanism for tRNA and retroviral RNA remodelling during primer annealing

naturejournals

# SHARE

**Download** the NatureJournals app for iPad, iPhone and iPod touch and subscribe to any journal in the app for just \$35.99\*. Tap in and discover more.

# nature.com/appforall







nature publishing group npg

# naure

## 27 November 2014 / Vol 515 / Issue No. 7528

### EDITORIAL

LONDON, PARIS, MUNICH, nature@nature.com SHANGHAI, TOKYO, SAN FRANCISCO, WASHINGTON DC, NEW YORK, BOSTON EDITOR-IN-CHIEF: Philip Campbell

NATURE EDITORIAL DIRECTOR: Ritu Dhand DIRECTOR, AUTHOR AND REVIEWER SERVICES: Véronique Kiermer

**EXECUTIVE EDITOR:** Nick Campbell HEAD OF EDITORIAL PRODUCTION: Lucy Banham

CHIEF MAGAZINE EDITOR: Rosie Mestel

**CREATIVE DIRECTOR:** Kelly Buckheit Krause THIS WEEK/NEWS/FEATURES: Alison Abbott, David Adam, Celeste Biever, Declan Butler, Ewen Callaway, Davide Castelvecchi, Erika Check Hayden, Matthew Crenson, Daniel Cressey, David Cyranoski, Elizabeth Gibney, Heidi Ledford, Corie Lok, Brendan Maher, Richard Monastersky, Lauren Morello, Anna Nagle, Helen Pearson, Sara Reardon, Quirin Schiermeier, Jeff Tollefson, Richard Van Noorden, M Mitchell Waldrop, Alexandra Witze COMMENT: Sara Abdulla, Joanne Baker, Rosalind Cotter, Barbara Kiser, Lucy Odling-Smee NATURE PODCAST/VIDEO: Charlotte Stoddart, Noah Baker, Kerri Smith NEWS AND VIEWS: Andrew Mitchinson, Jennifer Gardiner, Ana Lopes, Marian Turner RESEARCH: Francesca Cesari, Karl Ziemelis, I-han Chou, Tanguy Chouard, Rosamund Daw, Alex Eccleston, Angela Eggleston, Joshua Finkelstein, Henry Gee, Patrick Goymer, Hanna Granroth-Wilding, Noah Gray, Claire Hansell, Marie-Thérèse Heemels, Magdalena Helmer, Andrew Jermy, Nathalie Le Bot, Barbara Marte, Juliane Mössinger, Leonie Mueck, Leslie Sage, Sadaf Shadan, Mara Silva, Magdalena Skipper, Clare Thomas, John VanDecar, Liesbeth Venema, Ursula Weiss, Michael White INSIGHTS/ REVIEWS/PERSPECTIVES: Ursula Weiss CAREERS: Karen Kaplan TECHNOLOGY FEATURES: Vivien Marx FUTURES: Colin Sullivan SUPPLEMENTS: Herb Brody, Michelle Grayson, Kathryn Miller STATISTICAL ADVISER: Theresa Hyslop SUBEDITORS: Colin Sullivan, Mary Abraham, Sarah Archibald, Nicola Bailey, Adam Born, Nicolas Fanget, Isobel Flanagan, Paul Fletcher, Nisha Gaind, Anne Haggart, Dinah Loon, Anna Novitzky, Yukie Ozawa, Katherine Perry, David Price, Jenny Rooke, David Winters, Anna York PRODUCTION: Nick Kemp, Donald McDonald, Stewart Fraser, Susan Gray, Simon Gribbin, Hazel Mayhew, Ian Pope, Yvonne Strong, Roberta Tarran, Charles Wenz ART AND DESIGN: Wesley Fernandes, Michael Ayres, Jennifer Burns, Ffion Cleverley, Barbara Izdebska, Paul Jackman, Jasiek Krzysztofiak, Annthea Lewis, Chris Maddaloni, Chris Ryan, Nik Spencer, Claire Welsh JAPAN EDITION: Eiji Matsuda, Mika Ishida, Mitsuyo Utsugi, Sayaka Ayame PRESS OFFICE: Alice Henchley, Neda Afsarmanesh, Lisa Boucher, Sarah Lahert, Michael Stacey, Rebecca Walton NATURE DIGITAL: Tom Scott, Cianna Timbers, Alexander Thurrell, Dipti Shah, Dan Foley, Robert Sullivan, Matthew Carey, Luke Stavenhagen, Marta Rolak, Glynn Phillips, Marcin Arciuch ADMINISTRATION: Caroline McLean, Roseann Campbell, Emily Banham, Sophie Beasley, Emma Clifford, Dana Coles, Ella Kahn, Melissa Rose, Lauren Sequeira, Kenneth Simpson, Kimberly Tolleson, Michelle Viscuso, Andrea Von, Rebecca White, Diane Yorke

#### PUBLISHING

CHIEF EXECUTIVE OFFICER: Steven Inchcoombe PUBLISHER: Sarah Greaves

PUBLISHER (SUPPLEMENTS & PARTNERSHIPS): Richard Hughes PUBLISHING PROJECT MANAGER: Anastasia Panoutsou

CUSTOMER SERVICES	www.nature.com/help
REPRINTS	www.nature.com/reprints
ADVERTISING & SPONSORSHIP	www.nature.com/advertising

# DISPLAY ADVERTISING US/CANADA: display@us.nature.com

EUROPE: display@nature.com ASIA-PACIFIC: nature@natureasia.com SPONSORSHIP: sponsorship@nature.com NATURE JOBS: naturejobs@nature.com

464 | NATURE | VOL 515 | 27 NOVEMBER 2014

#### PRESS OFFICE

### MARKETING

USA/CANADA/LATIN AMERICA: marketing@us.nature.com EUROPE/REST OF WORLD: marketing@nature.com JAPAN/CHINA/KOREA: marketing@natureasia.com INDIA: marketing-india@nature.com

#### SITE LICENCES www.nature.com/libraries/site\_licences

A A I OCKEL

press@nature.com

n

0

d

b

n

N

0

W

P

W

AMERICAS: institutions@natureny.com ASIA-PACIFIC: institutions@natureasia.com AUSTRALIA/NEW ZEALAND: nature@macmillan.com.au EUROPE/ROW: institutions@nature.com INDIA: npgindia@nature.com

#### PERSONAL SUBSCRIPTIONS (INCLUDING POST AND PACKING) **UK/EUROPE/REST OF WORLD**

subscriptions@nature.com FULL RATE: UK £1,947; Europe €3,014 PERSONAL RATES: UK £135; Europe €209; Rest of World £210 STUDENT RATES: UK £79; Europe €122; Rest of World £125 Individual rates apply to payments by personal cheque or credit card. BACK ISSUES: £20.00.

#### **USA/CANADA/LATIN AMERICA** subscriptions@us.nature.com

INSTITUTIONAL/CORPORATE RATE: \$3,790 PERSONAL RATE: \$199 STUDENT RATE: \$99; POSTDOC RATE: \$119 Printed in USA. Individual rates available only to subscribers paying by personal check or credit card. Orders for student/postdoc subscriptions must be accompanied by a copy of student ID. Rates apply to USA, Canada, Mexico/Central & South America. Add 7% GST tax in Canada (Canadian GST number 140911595). BACK ISSUES: US\$20.00. JAPAN/CHINA/KOREA

JAPAN: nature.asia/japan-subscribe CHINA: nature.asia/china-subscribe KOREA: www.natureasia.com/ko-kr/subscribe

### MANAGEMENT OFFICES

NPG LONDON: nature@nature.com The Macmillan Building, 4 Crinan Street, London N1 9XW Tel: +44 (0)20 7833 4000

NPG NEW YORK: nature@natureny.com 75 Varick St, 9th Floor, New York, NY 10013-1917

Tel: +1 212 726 9200 NPG ASIA-PACIFIC: nature@natureasia.com Chiyoda Building, 2-37 Ichigayatamachi, Shinjuku-ku,

Tokyo 162-0843 Tel: +81 3 3267 8751 NPG GREATER CHINA: china@nature.com

42F-10/11, The Center, 989 Changle Lu, Shanghai 200031 Tel: +86 21 2422 5000

A list of other NPG offices can be found at www.nature.com/npg\_/contact/offices.html

# Nature® (ISSN 0028-0836) published weekly by – UK edition: Nature Publishing Group, a division of Macmillan Publishers Ltd, The Macmillan Building, 4 Crinan Street, London N1 9XW, UK.

US edition: Nature America, Inc. trading as Nature Publishing Group, 75 Varick St, 9th FI, New York NY 10013-1917, USA. Japan edition: NPG Asia-Pacific, Chiyoda Building, 2-37 Ichigayatamachi, Shinjuku-ku, Tokyo 162-0843, Japan. Registered as a newspaper at the British Post Office. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form (electronic or otherwise) without prior permission from permissions@nature.com. In the US, Nature (ISSN 0028-0836) is published weekly except the last week in December by Nature America, Inc. trading as Nature Publishing Group, 75 Varick St, 9th FI, New York NY 10013-1917, USA. US Periodicals postage paid at New York NY, and additional mailing post offices. US POSTMASTER: send address changes to Nature America, Inc. Subscription Dept, 75 Varick St, 9th FI, New York NY

10013-1917, USA

© 2014 Macmillan Publishers Limited. All rights reserved.

# DOCKET A L A R M



# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

# **Real-Time Litigation Alerts**



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

# **Advanced Docket Research**



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

# **Analytics At Your Fingertips**



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

# API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

# E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.