



## COVER

The many layers of gene regulation in a eukaryotic cell, envisioned as a video game. Transcription in the nucleus (green circle) proceeds to translation in the cytoplasm via genome topology, polymerase pausing, microRNA repression, RNA splicing, and riboswitch regulation. See the special section beginning on page 1781.

*Illustration: Carin L. Cain*

## DEPARTMENTS

- 1727 Science Online
- 1729 This Week in *Science*
- 1735 Editors' Choice
- 1738 Contact *Science*
- 1741 Random Samples
- 1743 Newsmakers
- 1775 AAAS News & Notes
- 1856 New Products
- 1857 Science Careers

## EDITORIAL

- 1733 Shortcuts to Medical Progress?  
*by Bruce Alberts*  
>> *Gene Regulation special section p. 1781*

## SPECIAL SECTION

# Gene Regulation

## INTRODUCTION

Freedom of Expression 1781

## NEWS

MicroRNAs Make Big Impression in Disease After Disease 1782

## PERSPECTIVES

Gene Regulation by Transcription Factors and MicroRNAs  
*O. Hobert* 1785

The Eukaryotic Genome as an RNA Machine  
*P. P. Amaral, M. E. Dinger, T. R. Mercer, J. S. Mattick* 1787

Multilevel Regulation of Gene Expression by MicroRNAs  
*E. V. Makeyev and T. Maniatis* 1789

Transcription Regulation Through Promoter-Proximal Pausing of RNA Polymerase II  
*L. J. Core and J. T. Lis* 1791

Gene Regulation in the Third Dimension  
*J. Dekker* 1793

Complex Riboswitches  
*R. R. Breaker* 1795

Evolution of Eukaryotic Transcription Circuits  
*B. B. Tuch, H. Li, A. D. Johnson* 1797

>> *Editorial p. 1733; for online content, see p. 1727 or go to [www.sciencemag.org/generegulation/](http://www.sciencemag.org/generegulation/)*



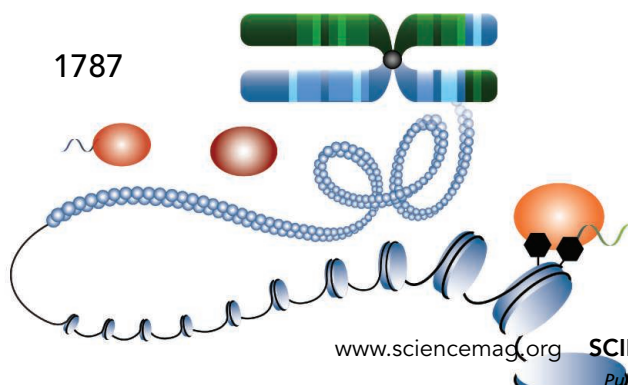
## NEWS OF THE WEEK

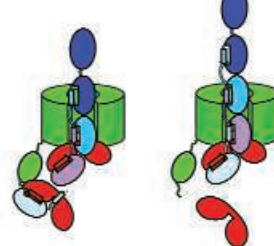
- Roads, Ports, Rails Aren't Ready for Changing Climate, Says Report 1744
- Study Fingers Soot as a Major Player in Global Warming 1745
- Smart Birds Lend a Beak for Food 1746
- NIH Reports Breach of Patient Records 1746
- Elusive Pathogen Cornered at Last 1747
- SCIENCESCOPE** 1747
- China's Modern Medical Minister 1748
- Saudi Start-Up Hopes Grants Will Buy Time 1748

## NEWS FOCUS

- Science by the Masses 1750
- Weighing the Climate Risks of an Untapped Fossil Fuel 1753
- With New Disease Genes, a Bounty of Questions 1754
- Lunar and Planetary Science Conference 1756
  - Cooking Up the Solar System From the Right Ingredients
  - New Piece of the Solar System Puzzle Fits In
  - What Was a 'Wet and Warm' Early Mars Really Like?
  - Snapshots From the Meeting

CONTENTS continued >>





## SCIENCE EXPRESS

[www.sciencexpress.org](http://www.sciencexpress.org)

### MATERIALS SCIENCE

#### Stretchable and Foldable Silicon Integrated Circuits

*D.-H. Kim et al.*

High-performance, bendable, and stretchable electronic devices are fabricated on an elastic plastic substrate by placing the critical electronic components in the neutral bending plane.

10.1126/science.1154367

### APPLIED PHYSICS

#### Silica-on-Silicon Waveguide Quantum Circuits

*A. Politi et al.*

Quantum circuits—in which individual photons interfere, entangle, and form logic gates—have been realized on silicon chips.

10.1126/science.1155441

### BIOCHEMISTRY

#### Reconstitution of Pilus Assembly Reveals a Bacterial Outer Membrane Catalyst

*M. Nishiyama, T. Ishikawa, H. Rechsteiner, R. Glockshuber*

The cell-free formation of the protruberant pilus of a pathogenic bacteria is accelerated by a protein that catalyzes supramolecular assembly without input of cellular energy.

10.1126/science.1154994

### GENETICS

#### Rare Structural Variants Disrupt Multiple Genes in Neurodevelopmental Pathways in Schizophrenia

*T. Walsh et al.*

Patients with schizophrenia carry multiple small deletions and duplications in their DNA that are associated nonrandomly with neuronal signaling and brain development pathways.

10.1126/science.1155174

## LETTERS

The Last Inventor of the Telephone *J. Schmidhuber* 1759

Thinking Outside the Reef *E. L. Peterson, M. Beger, Z. T. Richards*

Putting Ant-Acacia Mutualisms to the Fire  
*R. Cochard and D. Agosti* Response *T. M. Palmer et al.*

## BOOKS *ET AL.*

Proust Was a Neuroscientist *J. Lehrer*; 1763

Artscience Creativity in the Post-Google Generation  
*D. Edwards*, reviewed by *J. Labinger*

Victorian Popularizers of Science Designing Nature for New Audiences  
*B. Lightman*, reviewed by *P. J. Pauly* 1764

## POLICY FORUM

The Planet Debate Continues 1765  
*M. V. Sykes*



## PERSPECTIVES

Multitasking in Tissues and Materials 1767

*P. B. Messersmith* >> Report p. 1816

A Milestone in Time Keeping 1768

*D. Kleppner* >> Reports pp. 1805 and 1808

When a Commodity Is Not Exactly a Commodity 1769

*N. Folbre*

Recording Earth's Vital Signs 1771

*R. F. Keeling*

A Postgenomic Visual Icon 1772

*J. N. Weinstein*

## REVIEW

### MATERIALS SCIENCE

Doped Nanocrystals 1776

*D. J. Norris, A. L. Efros, S. C. Erwin*

## BREVIA

### PLANETARY SCIENCE

Dynamics of Saturn's South Polar Vortex 1801

*U. A. Dyudina et al.*

Observations from Cassini show that the cloud vortex at Saturn's south pole shares some features with hurricanes (such as an eye wall), but forms by a different mechanism.

## REPORTS

### ASTROPHYSICS

Magnetar-Like Emission from the Young Pulsar in Kes 75 1802

*F. P. Gavriil et al.*

A pulsar exhibits x-ray bursts like that seen only in magnetars, which have ultrahigh magnetic fields, implying that neutron stars exhibit a continuum of magnetic activity.

CONTENTS continued >>

REPORTS CONTINUED...

PHYSICS

**Sr Lattice Clock at  $1 \times 10^{-16}$  Fractional Uncertainty by Remote Optical Evaluation with a Ca Clock** 1805  
A. D. Ludlow et al.

Two clocks based on optical transitions in single trapped ions, set 4 kilometers apart, are able to keep time within a fractional error of  $1 \times 10^{-16}$ , better than the standard atomic clock.

>> *Perspective p. 1768*

PHYSICS

**Frequency Ratio of Al<sup>+</sup> and Hg<sup>+</sup> Single-Ion Optical Clocks; Metrology at the 17th Decimal Place** 1808  
T. Rosenband et al.

Precise measurements of the frequency ratio of two optical clocks indicate that the fine-structure constant is fine and constant to an uncertainty of  $10^{-17}$ . >> *Perspective p. 1768*

CHEMISTRY

**Self-Assembly of Large and Small Molecules into Hierarchically Ordered Sacs and Membranes** 1812  
R. M. Capito et al.

Mixing of a high-molecular weight polymer with a low-molecular weight peptide amphiphile instantly forms repairable membrane sacs large enough to encapsulate cells.

MATERIALS SCIENCE

**The Transition from Stiff to Compliant Materials in Squid Beaks** 1816  
A. Miserez, T. Schneberk, C. Sun, F. W. Zok, J. H. Waite

The squid beak, sharp and hard only at the tip, exhibits a chemical gradient that tailors its mechanical properties to prevent damage to the attached soft muscle tissue. >> *Perspective p. 1767*

CHEMISTRY

**Determining Transition-State Geometries in Liquids Using 2D-IR** 1820  
J. F. Cahoon, K. R. Sawyer, J. P. Schlegel, C. B. Harris

Tracking vibrational modes through a transition state by spectroscopy reveals an iron compound's thermal ligand rearrangement, which was previously too fast to monitor.

CHEMISTRY

**Surface Trapping of Atoms and Molecules with Dipole Rings** 1824  
H. Dil et al.

Holes in a boron nitride surface ringed by in-plane dipoles form a nanometer-scale pore network with a trapping potential that can hold weakly adsorbed molecules.

MOLECULAR BIOLOGY

**Nutritional Control of Reproductive Status in Honeybees via DNA Methylation** 1827  
R. Kucharski, J. Maleszka, S. Foret, R. Maleszka

Epigenetic modifications that involve methylation cause female honeybee larvae to become queens rather than workers when they are fed royal jelly.

STRUCTURAL BIOLOGY

**The Flavivirus Precursor Membrane-Envelope Protein Complex: Structure and Maturation** 1830  
L. Li et al.

**Structure of the Immature Dengue Virus at Low pH Primes Proteolytic Maturation** 1834  
I.-M. Yu et al.

Dengue and West Nile viruses mature when the envelope protein precursor is cleaved at low pH, and then the cleavage product dissociates outside the cell, allowing infection.

NEUROSCIENCE

**Insect Odorant Receptors Are Molecular Targets of the Insect Repellent DEET** 1838  
M. Ditzen, M. Pellegrino, L. B. Vosshall

The widely used insect repellent DEET acts by inhibiting olfactory neurons that respond to odors such as those that attract insects to their hosts.

NEUROSCIENCE

**Aversive Learning Enhances Perceptual and Cortical Discrimination of Indiscriminable Odor Cues** 1842  
W. Li, J. D. Howard, T. B. Parrish, J. A. Gottfried

After association of negative stimuli to one of a pair of initially indistinguishable odors, human participants learn to tell the two odors apart and show altered brain representations.

NEUROSCIENCE

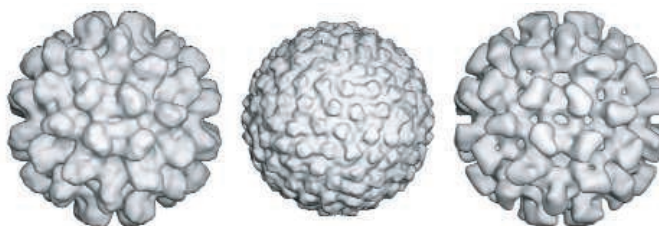
**Electric Fields Due to Synaptic Currents Sharpen Excitatory Transmission** 1845  
S. Silyantsev et al.

The electrical field set up by currents within the synaptic cleft can influence diffusion of negatively charged neurotransmitters, such as glutamate, and prolong excitatory events.

NEUROSCIENCE

**Rule Learning by Rats** 1849  
R. A. Murphy, E. Mondragón, V. A. Murphy

Rats can learn the rules governing simple sequences of stimuli and then unexpectedly can generalize these rules to new situations.



1834

SCIENCE (ISSN 0036-8075) is published weekly on Friday, except the last week in December, by the American Association for the Advancement of Science, 1200 New York Avenue, NW, Washington, DC 20005. Periodicals Mail postage (publication No. 484460) paid at Washington, DC, and additional mailing offices. Copyright © 2008 by the American Association for the Advancement of Science. The title SCIENCE is a registered trademark of the AAAS. Domestic individual membership and subscription (51 issues): \$144 (\$74 allocated to subscription). Domestic institutional subscription (51 issues): \$770; Foreign postage extra: Mexico, Caribbean (surface mail) \$55; other countries (air assist delivery) \$85. First class, airmail, student, and emeritus rates on request. Canadian rates with GST available upon request, GST #1254 88122. Publications Mail Agreement Number 1069624. SCIENCE is printed on 30 percent post-consumer recycled paper. Printed in the U.S.A.



ADVANCING SCIENCE. SERVING SOCIETY

Change of address: Allow 4 weeks, giving old and new addresses and 8-digit account number. Postmaster: Send change of address to AAAS, P.O. Box 96178, Washington, DC 20090-6178. Single-copy sales: \$10.00 current issue, \$15.00 back issue prepaid includes surface postage; bulk rates on request. Authorization to photocopy material for internal or personal use under circumstances not falling within the fair use provisions of the Copyright Act is granted by AAAS to libraries and other users registered with the Copyright Clearance Center (CCC) Transactional Reporting Service, provided that \$20.00 per article is paid directly to CCC, 222 Rosewood Drive, Danvers, MA 01923. The identification code for Science is 0036-8075. Science is indexed in the Reader's Guide to Periodical Literature and in several specialized indexes.

CONTENTS continued >>>



The eyes have it.

## SCIENCE NOW

[www.sciencenow.org](http://www.sciencenow.org) DAILY NEWS COVERAGE

### New Form of Vision Discovered

Mantis shrimp eyes can see circular polarized light, which may be used in mating or secret signaling.

### Therapeutic Cloning Shows Promise for Parkinson's Disease

Mice treated with their own cells.

### What Does a Plant Sound Like?

A computer program reveals how bats find their favorite foliage—and how we can use the same trick.



The hazards of perfectionism.

## SCIENCE CAREERS

[www.sciencecareers.org/career\\_development](http://www.sciencecareers.org/career_development)

CAREER RESOURCES FOR SCIENTISTS

### Mind Matters: Too Perfect?

*I. S. Levine*

Perfectionism can diminish productivity, undermine job satisfaction, and damage work relationships.

### Mastering Your Ph.D.: Goodbye to All That

*P. Gosling and B. Noordam*

Once you've said goodbye to the bench, you can take comfort in the opportunities that await.

### Educated Woman, Postdoc Edition, Chapter 14: Interview Excursions

*M. P. DeWhyse*

It's official: Micella is out shopping for a new career.

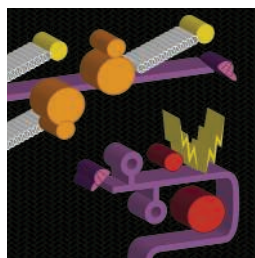
### From the Archives: Thanks for the Great Postdoc Bargain

*R. Freeman*

The Harvard economist thanks postdocs for their skilled and diligent servitude.

## SPECIAL SECTION

# Gene Regulation



## SCIENCE SIGNALING

[www.stke.org](http://www.stke.org) THE SIGNAL TRANSDUCTION KNOWLEDGE ENVIRONMENT

### EDITORIAL GUIDE: Focus Issue—Mechanisms of Gene Regulation

*J. F. Foley*

Multilayered mechanisms control various aspects of gene expression.

### PERSPECTIVE: Silent Assassin—Oncogenic Ras Directs Epigenetic Inactivation of Target Genes

*X. Cheng*

Oncogenic Ras directs a program that epigenetically silences genes that inhibit tumorigenesis.

### PERSPECTIVE: NFAT Is Well Placed to Direct Both Enhancer Looping and Domain-Wide Models of Enhancer Function

*P. N. Cockerill*

Inducible intrachromosomal looping between the tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) gene promoter and two NFAT-dependent enhancers activates TNF- $\alpha$  gene expression.

### PERSPECTIVE: SRC-3 Transcription-Coupled Activation, Degradation, and the Ubiquitin Clock—Is There Enough Coactivator to Go Around in Cells?

*D. M. Lonard and B. W. O'Malley*

The critical factor in estrogen-dependent growth of breast cancer cells appears to be the abundance of the coactivator protein SRC-3.

## SCIENCE PODCAST

Download the 28 March *Science* Podcast to hear about rule learning by rats, the biomechanical properties of squid beaks, making sense of genome-wide association studies, and more.

[www.sciencemag.org/about/podcast.dtl](http://www.sciencemag.org/about/podcast.dtl)



Separate individual or institutional subscriptions to these products may be required for full-text access.

# Science

**319 (5871)**

*Science* **319** (5871), 1729-1861.

**ARTICLE TOOLS**

<http://science.sciencemag.org/content/319/5871>

**PERMISSIONS**

<http://www.sciencemag.org/help/reprints-and-permissions>

Use of this article is subject to the [Terms of Service](#)

---

*Science* (print ISSN 0036-8075; online ISSN 1095-9203) is published by the American Association for the Advancement of Science, 1200 New York Avenue NW, Washington, DC 20005. The title *Science* is a registered trademark of AAAS.

Copyright © 2008 The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. No claim to original U.S. Government Works.