

Science.
v. 349, no. 6246 (July 24 2015)
Reference Collection
W1 SC653
2015-08-13 13:10:39

...ut the range of
fibers pp. 382 & 400

Regulating emerging
technologies p. 384

Science

\$10
24 JULY 2015
sciencemag.org

AAAS



PROPERTY OF THE
NATIONAL
LIBRARY OF
MEDICINE

*Unlocking
the past*

Ancient DNA comes
of age p. 358

**DOCKET
ALARM**

Find authenticated court documents without watermarks at docketalarm.com.

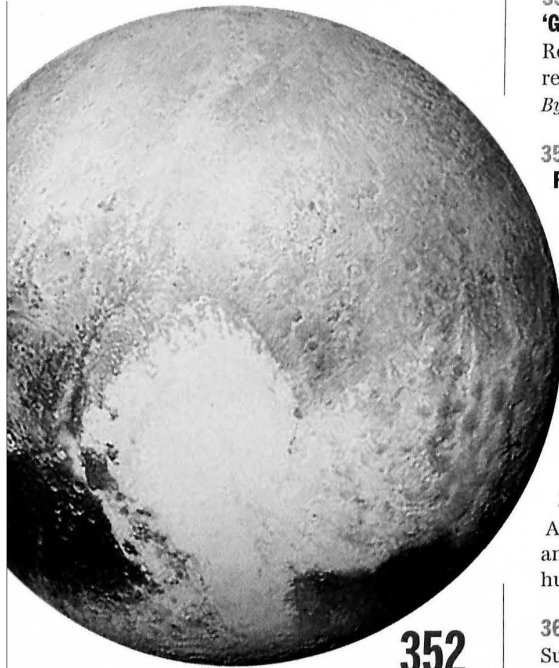
CONTENTS

24 JULY 2015 • VOLUME 349 • ISSUE 6246



386

Toward an HIV vaccine



352

NEWS

IN BRIEF

350 Roundup of the week's news

IN DEPTH

352 SCIENTISTS PONDER AN IMPROBABLY ACTIVE PLUTO

New Horizons delights researchers with stark vistas and perplexing puzzles
By E. Hand

354 NEW MYSTERY FOR NATIVE AMERICAN ORIGINS

Rival papers compete to explain surprising link to Australia and Melanesia
By M. Balter

► RESEARCH ARTICLE BY M. RAGHAVAN ET AL.
10.1126/science.aab3884

355 CHILD FIGHTS HIV TO A DRAW

After 12 years off treatment, a young woman has had remarkable—and unexplained—control of her infection
By J. Cohen

356 IRAN NUCLEAR DEAL HOLDS 'GOODIES' FOR SCIENTISTS

Researchers to collaborate at repurposed nuclear facilities
By R. Stone

357 WEB BILLIONAIRE JOINS SEARCH FOR ALIEN SIGNALS

Yuri Milner hopes that \$100 million can answer one of humanity's most enduring questions
By D. Clery

FEATURES

358 NEW LIFE FOR OLD BONES

After a stormy adolescence, the field of ancient DNA enters its golden era
By E. Culotta

► PODCAST

362 REVOLUTION IN HUMAN EVOLUTION

As it smashes disciplinary boundaries, ancient DNA is rewriting much of human prehistory
By A. Gibbons

367 LOST WORLDS FOUND

Sugar cubes of buried soil reveal how ecosystems warmed after the last ice age
By E. Pennisi

369 Prospecting for genetic gold

By E. Pennisi

► BOOKS ET AL. P. 388; VIDEO

► RESEARCH ARTICLE BY A. COOPER ET AL.
10.1126/science.aac4315

370 BREAKING A TROPICAL TABOO

Most ancient DNA comes from frigid environs. Can new methods sample hot and humid locales?
By L. Wade

372 PROTEIN POWER

Paleoproteomics hustles to catch up with its more developed cousin
By R. F. Service



372

This material was copied

INSIGHTS

PERSPECTIVES

374 FOUR LEGS TOO MANY?

A long-bodied fossil snake retains fore- and hindlimbs
By S. Evans
► REPORT P. 415

376 MAKING METHANE DOWN DEEP

Scientists find active life 2.5 km beneath the sea floor
By J. A. Huber
► REPORT P. 420

377 MOVING CTLA-4 FROM THE TRASH TO RECYCLING

Individuals lacking a protein expressed in T cells have low CTLA-4 and develop autoimmunity
By D. M. Sansom
► REPORT P. 436

379 CATALYSTS BY PLATONIC DESIGN

Sophisticated shape-controlled design is yielding ever more active nanocatalysts
By P. Strasser
► REPORT P. 412

380 BREAKERS AND BLOCKERS—miRNAs AT WORK

MicroRNAs mediate silencing through messenger RNA degradation and translation repression
By E. Izaurralde

382 STRETCH, WRAP, AND RELAX TO SMARTNESS

Carbon nanotubes wrapped around rubber cores create resilient conducting fibers
By T. Ghosh
► REPORT P. 400

384 YELLOW LIGHTS FOR EMERGING TECHNOLOGIES

All-or-none regulatory systems are not adequate for revolutionary innovations
By R. A. Charo

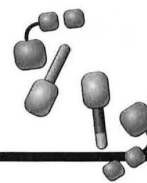
386 TOWARD AN HIV VACCINE: A SCIENTIFIC JOURNEY

Different strategies are coming together to provide insights for an effective HIV vaccine
By A. S. Fauci and H. D. Marston



374 & 416

A Cretaceous snake with limbs



377 & 436

An autoimmunity mechanism

BOOKS ET AL.

388 HOW TO CLONE A MAMMOTH

By B. Shapiro, reviewed by A. R. Hoelzel

► NEWS STORY P. 369

389 THE LOCK AND KEY OF MEDICINE

By L. V. Marks, reviewed by S. Prabhakaran

LETTERS

390 PRECISION MEDICINE: LOOK TO THE MICE

By K. C. K. Lloyd et al.

390 SEXISM DISCUSSION MISSES THE POINT

By H. S. Young

391 CHIMPANZEES DESERVE THEIR FREEDOM

By S. M. Wise

391 TECHNICAL COMMENT ABSTRACTS

RESEARCH

IN BRIEF

392 From Science and other journals

REVIEW

395 HUMAN MICROBIOTA

Small molecules from the human microbiota M. S. Donia and M. A. Fischbach

REVIEW SUMMARY; FOR FULL TEXT: dx.doi.org/10.1126/science.1254766

REPORTS

396 APPLIED ORIGAMI

Origami of thick panels Y. Chen et al.

400 STRETCHY ELECTRONICS

Hierarchically buckled sheath-core fibers for superelastic electronics, sensors, and muscles Z. F. Liu et al.

► PERSPECTIVE P. 382

392



QUANTUM INFORMATION

405 Coherent coupling between a ferromagnetic magnon and a superconducting qubit Y. Tabuchi et al.

408 Coherent coupling of a single spin to microwave cavity photons J. J. Viennot et al.

412 NANOCATALYSTS

Platinum-based nanocages with subnanometer-thick walls and well-defined, controllable facets L. Zhang et al. ► PERSPECTIVE P. 379

416 EVOLUTION

A four-legged snake from the Early Cretaceous of Gondwana D. M. Martill et al. ► PERSPECTIVE P. 374

420 DEEP BIOSPHERE

Exploring deep microbial life in coal-bearing sediment down to ~2.5 km below the ocean floor F. Inagaki et al. ► PERSPECTIVE P. 376

424 NEURODEVELOPMENT

Adult cortical plasticity depends on an early postnatal critical period S. D. Greenhill et al.

INTRACELLULAR TRANSPORT

428 PI4P/phosphatidylserine countertransport at ORP5- and ORP8-mediated ER-plasma membrane contacts J. Chung et al.

432 Phosphatidylserine transport by ORP/Osh proteins is driven by phosphatidylinositol 4-phosphate J. Moser von Filseck et al.

436 AUTOIMMUNE DISEASE

Patients with LRBA deficiency show CTLA4 loss and immune dysregulation responsive to abatacept therapy B. Lo et al. ► PERSPECTIVE P. 377

DEPARTMENTS

349 EDITORIAL

Rethinking graduate education By Alan I. Leshner

446 WORKING LIFE

Songwriting and science By C. Neal Stewart Jr.

ON THE COVER



A researcher drills into ancient bone to extract material for DNA analysis at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany. As the newest sequencing methods are applied to ancient samples and spread to many laboratories, ancient DNA is poised to enter its golden age, delivering stunning results ranging from the evolution of humans to that of microbes. See page 358. Photo: © Jörg Singer

Science Staff 348
New Products 441
Science Careers 442

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 © 2015 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): \$153 (\$74 allocated to subscription). Domestic institutional subscription (51 issues): \$1282; 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 #R1254-88122, Publications Mail Agreement Number 1069624. Printed in the U.S.A. Change of address: Allow 4 weeks, giving old and new addresses and 3-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 \$3.00 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.

Editor-in-Chief Marcia McNutt

Executive Editor Monica M. Bradford **News Editor** Tim Appenzeller

Managing Editor, Research Journals Katrina L. Kelner

Deputy Editors Barbara R. Jasny, Andrew M. Sugden(UK), Valda J. Vinson, Jake S. Yeston

Research and Insights

SR. EDITORS Caroline Ash(UK), Gilbert J. Chin, Lisa D. Chong, Julia Fahrenkamp-Uppenbrink(UK), Pamela J. Hines, Stella M. Hurlley(UK), Paula A. Kiberstis, Marc S. Lavine(Canada), Kristen L. Mueller, Ian S. Osborne(UK), Beverly A. Purnell, L. Bryan Ray, Guy Riddiough, H. Jesse Smith, Jelena Stajic, Peter Stern(UK), Phillip D. Szuromi, Brad Wible, Nicholas S. Wigginton, Laura M. Zahn **ASSOCIATE EDITORS** Brent Grocholski, Keith T. Smith, Sacha Vignieri **ASSOCIATE BOOK REVIEW EDITOR** Valerie B. Thompson **ASSOCIATE LETTERS EDITOR** Jennifer Silis **CHIEF CONTENT PRODUCTION EDITOR** Cara Tate **SR. CONTENT PRODUCTION EDITORS** Harry Jach **CONTENT PRODUCTION EDITORS** Jeffrey E. Cook, Chris Filiatreau, Cynthia Howe, Lauren Kmeo, Barbara P. Ordway, Catherine Wolner **SR. EDITORIAL COORDINATORS** Carolyn Kyle, Beverly Shields **EDITORIAL COORDINATORS** Ramatoulaye Diop, Joi S. Granger, Lisa Johnson, Anita Wynn **PUBLICATIONS ASSISTANTS** Aneera Dobbins, Jeffrey Hearn, Dona Mathieu, Le-Toya Mayne Flood, Shannon McMahon, Scott Miller, Jerry Richardson, Rachel Roberts(UK), Alice Whaley(UK), Brian White **EXECUTIVE ASSISTANT** Anna Bashkirova **ADMINISTRATIVE SUPPORT** Janet Clements(UK), Lizanne Newton(UK), Maryrose Madrid, Laura-Nadine Schuhmacher (UK, Intern), Alix Welch (Intern), John Wood(UK)

News

NEWS MANAGING EDITOR John Travis **INTERNATIONAL EDITOR** Richard Stone **DEPUTY NEWS EDITORS** Daniel Clery(UK), Robert Coontz, Elizabeth Culotta, David Grimm, David Malakoff, Leslie Roberts **CONTRIBUTING EDITOR** Martin Enserink(Europe) **SR. CORRESPONDENTS** Jeffrey Mervis, Elizabeth Pennisi **NEWS WRITERS** Adrian Cho, Jon Cohen, Jennifer Couzin-Frankel, Carolyn Gramling, Eric Hand, Jocelyn Kaiser, Catherine Maticic, Kelly Servick, Robert F. Service, Erik Stokstad(Cambridge, UK), Emily Underwood **INTERNS** Emily Conover, Emily DeMarco, Annick Laurent, Laura Olivier, Juan David Romero **CONTRIBUTING CORRESPONDENTS** Michael Balter(Paris), John Bohannon, Ann Gibbons, Mara Hvistendahl, Sam Kean, Richard A. Kerr, Eli Kintisch, Kai Kupferschmidt(Berlin), Andrew Lawler, Christina Larson(Beijing), Mitch Leslie, Charles C. Mann, Eliot Marshall, Virginia Morell, Dennis Normile(Tokyo), Heather Pringle, Tania Rabesandratana(London), Gretchen Vogel(Berlin), Lizzie Wade(Mexico City) **CAREERS** Jim Austin(Editor), Donisha Adams, Rachel Bernstein **COPY EDITORS** Kara Estelle (Chief), Julia Cole, Jennifer Levin **ADMINISTRATIVE SUPPORT** Jessica Williams

Executive Publisher Rush D. Holt

Publisher Kent R. Anderson **Chief Digital Media Officer** Rob Covey

BUSINESS OPERATIONS AND PORTFOLIO MANAGEMENT DIRECTOR Sarah Whalen **BUSINESS SYSTEMS AND FINANCIAL ANALYSIS DIRECTOR** Randy Yi **MANAGER OF FULFILLMENT SYSTEMS** Neal Hawkins **SYSTEMS ANALYST** Nicole Mehmedovich **ASSISTANT DIRECTOR, BUSINESS OPERATIONS** Eric Knott **MANAGER, BUSINESS OPERATIONS** Jessica Tierney **BUSINESS ANALYSTS** Cory Lipman, Cooper Tilton, Celeste Troxler **FINANCIAL ANALYST** Robert Clark **RIGHTS AND PERMISSIONS ASSISTANT DIRECTOR** Emilie David **PERMISSIONS ASSOCIATE** Elizabeth Sandler **RIGHTS, CONTRACTS, AND LICENSING ASSOCIATE** Lili Kiser

MARKETING DIRECTOR Ian King **MARKETING MANAGER** Julianne Wielga **MARKETING ASSOCIATE** Elizabeth Sattler **SR. MARKETING EXECUTIVE** Jennifer Reeves **SR. ART ASSOCIATE, PROJECT MANAGER** Tzeitel Sorrosa **ART ASSOCIATE** Seil Lee **JR. ART ASSOCIATE** Kim Huynh **ASSISTANT COMMERCIAL EDITOR** Selby Frame **MARKETING PROJECT MANAGER** Angelisa McArthur **PROGRAM DIRECTOR** AAAS **MEMBER CENTRAL** Peggy Mihelich **FULFILLMENT SYSTEMS AND OPERATIONS** membership@aaas.org **MANAGER, MEMBER SERVICES** Pat Butler **SPECIALISTS** LaToya Casteel, Terrance Morrison, Latasha Russell **MANAGER, DATA ENTRY** Mickie Napoleoni **DATA ENTRY SPECIALISTS** JJ Regan, Brenden Aquilino, Fiona Giblin

DIRECTOR, SITE LICENSING Tom Ryan **DIRECTOR, CORPORATE RELATIONS** Eileen Bernadette Moran **SR. PUBLISHER RELATIONS SPECIALIST** Kiki Forsyth **PUBLISHER RELATIONS MANAGER** Catherine Holland **PUBLISHER RELATIONS, EASTERN REGION** Keith Layson **PUBLISHER RELATIONS, WESTERN REGION** Ryan Rexroth **SR. RESEARCH COORDINATOR** Aiesha Marshall **MANAGER, SITE LICENSE OPERATIONS** Iqou Edim **SENIOR PRODUCTION SPECIALIST** Robert Koepke **SENIOR OPERATIONS ANALYST** Lana Guz **FULFILLMENT ANALYST** Judy Lillbridge **ASSOCIATE DIRECTOR, MARKETING** Christina Schlicht **MARKETING ASSOCIATES** Thomas Landreth, Isa Sesay-Bah

DIRECTOR OF WEB TECHNOLOGIES Ahmed Khadr **SR. DEVELOPER** Chris Coleman **DEVELOPERS** Dan Berger, Jimmy Marks **SR. PROJECT MANAGER** Trista Smith **SYSTEMS ENGINEER** Luke Johnson

CREATIVE DIRECTOR, MULTIMEDIA Martyn Green **DIRECTOR OF ANALYTICS** Enrique Gonzales **SR. WEB PRODUCER** Sarah Crespi **WEB PRODUCER** Alison Crawford **VIDEO PRODUCER** Nguyen Nguyen **SOCIAL MEDIA PRODUCER** Meghna Sachdev

DIRECTOR OF OPERATIONS PRINT AND ONLINE Lizabeth Harman **DIGITAL/PRINT STRATEGY MANAGER** Jason Hillman **QUALITY TECHNICAL MANAGER** Marcus Spiegler **DIGITAL PRODUCTION MANAGER** Lisa Stanford **ASSISTANT MANAGER DIGITAL/PRINT** Rebecca Doshi **DIGITAL MEDIA SPECIALIST** Tara Kelly **SENIOR CONTENT SPECIALISTS** Steve Forrester, Antoinette Hodal, Lori Murphy, Anthony Rosen **CONTENT SPECIALISTS** Jacob Hedrick, Kimberley Oster

DESIGN DIRECTOR Beth Rakouskas **DESIGN EDITOR** Marcy Atarod **SENIOR SCIENTIFIC ILLUSTRATORS** Chris Bickel, Katharine Sutliff **SCIENTIFIC ILLUSTRATOR** Valerie Altounian **SENIOR ART ASSOCIATES** Holly Bishop, Preston Huey **SENIOR DESIGNER** Garvin Grullon **DESIGNER** Chrystal Smith **SENIOR PHOTO EDITOR** William Douthitt **PHOTO EDITORS** Leslie Blizard, Christy Steele

DIRECTOR, GLOBAL COLLABORATION, CUSTOM PUBLICATIONS, ADVERTISING Bill Moran **EDITOR, CUSTOM PUBLISHING** Sean Sanders: 202-326-6430 **ASSISTANT EDITOR, CUSTOM PUBLISHING** Tianna Hicklin: 202-326-6463 **ADVERTISING MARKETING MANAGER** Justin Sawyer: 202-326-7061 **science_advertising@aaas.org** **ADVERTISING MARKETING ASSOCIATE** Javia Flemmings **ADVERTISING SUPPORT MANAGER** Karen Foyle: 202-326-6740 **ADVERTISING PRODUCTION OPERATIONS MANAGER** Deborah Tompkins **SR. PRODUCTION SPECIALIST/GRAPHIC DESIGNER** Amy Hardcastle **PRODUCTION SPECIALIST** Yuse Lajiminhup **SR. TRAFFIC ASSOCIATE** Christine Hill **SALES COORDINATOR** Shirley Young **ASSOCIATE DIRECTOR, COLLABORATION, CUSTOM PUBLICATIONS/CHINA/TAIWAN/KOREA/SINGAPORE** Ruolei Wu: +86-186 0822 9345, rwu@aaas.org **COLLABORATION/CUSTOM PUBLICATIONS/JAPAN** Adarsh Sandhu + 81532-81-5442, asandhu@aaas.org **EAST COAST/E. CANADA** Laurie Faraday: 508-747-9395, FAX 617-507-8189 **WEST COAST/W. CANADA** Lynne Stickrod: 415-931-9782, FAX 415-520-6940 **MIDWEST** Jeffrey Dembski: 847-498-4520 x3005, Steven Loerch: 847-498-4520 x3006 **UK EUROPE/ASIA** Roger Goncalves: TEL/FAX +41 43 243 1358 **JAPAN** Katsuyoshi Fukamizu (Tokyo): +81-3-3219-5777 **klukamizu@aaas.org** **CHINA/TAIWAN** Ruolei Wu: +86-186 0822 9345, rwu@aaas.org

WORLDWIDE ASSOCIATE DIRECTOR OF SCIENCE CAREERS Tracy Holmes: +44 (0) 1223 326525, FAX +44 (0) 1223 326532 **trholmes@science-int.co.uk** **CLASSIFIED** **advertising@sciencecareers.org** **U.S. SALES** Tina Burks: 202-326-6577, Nancy Toema: 202-326-6578 **SALES ADMINISTRATOR** Marci Gallun **EUROPE/ROW SALES** Axel Gesatzki, Sarah Lelarge **SALES ASSISTANT** Kelly Grace **JAPAN** Hiroyuki Mashiki (Kyoto): +81-75-823-1109 **hmashiki@aaas.org** **CHINA/TAIWAN** Ruolei Wu: +86-186 0822 9345, rwu@aaas.org **MARKETING MANAGER** Allison Pritchard **MARKETING ASSOCIATE** Aimee Aponte

AAAS BOARD OF DIRECTORS **RETIRING PRESIDENT** Gerald R. Fink **PRESIDENT** Geraldine (Ger) Richmond **PRESIDENT-ELECT** Barbara A. Schaal **TREASURER** David Evans **SHAW CHIEF EXECUTIVE OFFICER** Rush D. Holt **BOARD** Bonnie L. Bassler, May R. Berenbaum, Carlos J. Bustamante, Stephen P.A. Fodor, Claire M. Fraser, Michael S. Gazzaniga, Laura H. Greene, Elizabeth Loftus, Mercedes Pascual

SUBSCRIPTION SERVICES For change of address, missing issues, and payment questions: 866-434-AAAS (2227) or 202-326-6417, FAX 202-842-1055. Mailing addresses: AAAS, P.O. Box 95178, Washington, DC 20099-6178 or AAAS Member Services, 1200 New York Avenue, NW, Washington, DC 20005

INSTITUTIONAL SITE LICENSES 202-326-6755 **REPRINTS**: Author Inquiries 800-635-7181 **COMMERCIAL INQUIRIES** 803-359-4578 **PERMISSIONS** 202-326-6765, **permissions@aaas.org** **AAAS Member Services** 202-326-6417 or <http://membercentral.aaas.org/discuss>

Science serves as a forum for discussion of important issues related to the advancement of science by publishing material on which a consensus has been reached as well as including the presentation of minority or conflicting points of view. Accordingly, all articles published in Science—including editorials, news and comment, and books reviews—are signed and reflect the individual views of the authors and not official points of view adopted by AAAS or the institutions with which the authors are affiliated.

INFORMATION FOR AUTHORS See pages 678 and 679 of the 6 February 2015 issue or access www.sciencemag.org/about/authors

SENIOR EDITORIAL BOARD

Robert H. Grubbs, *California Institute of Technology*, Gary King, *Harvard University*
Susan M. Rosenberg, *Baylor College of Medicine*, Ali Shalita, *Northwestern University*
Feinberg School of Medicine, Michael S. Turner, *U. of Chicago*

BOARD OF REVIEWING EDITORS (Statistics board members indicated with \$)

Adriano Aguzzi, *U. Hospital Zurich*
Takuzo Aida, *U. of Tokyo*
Leslie Aiello, *Wenner-Gren Foundation*
Judith Allen, *U. of Edinburgh*
Sonia Altizer, *U. of Georgia*
Sebastian Amigorena, *Institut Curie*
Kathryn Anderson, *Memorial Sloan Kettering Cancer Center*
Meinrat O. Andreea, *Max Planck Inst. Mainz*
Paola Arlotta, *Harvard U.*
Johan Auwerx, *EPFL*
David Awschalom, *U. of Chicago*
Jordi Bascompte, *Estación Biológica de Doñana CSIC*
Facundo Batista, *London Research Inst.*
Ray H. Baughman, *U. of Texas, Dallas*
David Baum, *U. of Wisconsin*
Carlo Beenakker, *Leiden U.*
Kamran Behnia, *ESPCI ParisTech*
Yasmine Belkaid, *NIAID, NIH*
Philip Benfey, *Duke U.*
Stephen J. Benkovic, *Penn State U.*
May Berenbaum, *U. of Illinois*
Gabriele Bergers, *U. of California, San Francisco*
Bradley Bernstein, *Massachusetts General Hospital*
Peer Bork, *EMBL*
Bernard Bourdon, *Ecole Normale Supérieure de Lyon*
Chris Bowler, *Ecole Normale Supérieure*
Ian Boyd, *U. of St. Andrews*
Emily Brodsky, *U. of California, Santa Cruz*
Ron Brookmeyer, *U. of California Los Angeles (\$)*
Christian Büchel, *U. Hamburg-Eppendorf*
Joseph A. Burns, *Cornell U.*
György Buzsáki, *New York U. School of Medicine*
Nicola Caporali, *Duke U.*
Mats Carlsson, *U. of Oslo*
David Clapham, *Children's Hospital Boston*
David Clary, *U. of Oxford*
Joel Cohen, *Rockefeller U., Columbia U.*
James Collins, *Boston U.*
Robert Cook-Deegan, *Duke U.*
Alan Cowman, *Walter & Eliza Hall Inst.*
Robert H. Crabtree, *Yale U.*
Roberta Croce, *Vrije Universiteit*
Janet Currie, *Princeton U.*
Jeff L. Dangl, *U. of North Carolina*
Tom Daniell, *U. of Washington*
Frans de Waal, *Emory U.*
Stanislas Dehaene, *Collège de France*
Robert Desimone, *MIT*
Claude Desplan, *New York U.*
Ap Dijksterhuis, *Radboud U. of Nijmegen*
Dennis Discher, *U. of Pennsylvania*
Gerald W. Dorn II, *Washington U. School of Medicine*
Jennifer A. Doudna, *U. of California, Berkeley*
Bruce Dunn, *U. of California, Los Angeles*
Christopher Dye, *WHO*
Todd Ehlers, *U. of Tuebingen*
David Ehrhard, *Carnegie Inst. of Washington*
Tim Elston, *U. of North Carolina at Chapel Hill*
Gerhard Ertl, *Fritz-Haber Institut, Berlin*
Barry Everitt, *U. of Cambridge*
Ernst Fehr, *U. of Zurich*
Anne C. Ferguson-Smith, *U. of Cambridge*
Michael Feuer, *The George Washington U.*
Toren Finkel, *NIH, NIH*
Kate Fitzgerald, *U. of Massachusetts*
Peter Fratzl, *Max Planck Inst.*
Elaine Fuchs, *Rockefeller U.*
Daniel Geschwind, *UCIA*
Andrew Gewirth, *U. of Illinois*
Karl-Heinz Glassmeier, *U. Braunschweig*
Ramon Gonzalez, *Rice U.*
Julia R. Greer, *Caltech*
Elizabeth Grove, *U. of Chicago*
Nicolas Gruber, *EHR Zurich*
Kip Guy, *St. Jude's Children's Research Hospital*
Taekjip Ha, *U. of Illinois at Urbana-Champaign*
Christian Haass, *Ludwig Maximilians U.*
Steven Hahn, *Fred Hutchinson Cancer Research Center*
Michael Hasselmo, *Boston U.*
Martin Heimann, *Max Planck Inst. Jena*
Yka Helariutta, *U. of Cambridge*
James A. Hendler, *Rensselaer Polytechnic Inst.*
Janet G. Hering, *Swiss Fed. Inst. of Aquatic Science & Technology*
Kai-Uwe Hinrichs, *U. of Bremen*
Kei Hirose, *Tokyo Inst. of Technology*
David Hodell, *U. of Cambridge*
David Holden, *Imperial College*
Lora Hooper, *UT Southwestern Medical Ctr. at Dallas*
Raymond Huey, *U. of Washington*
Steven Jacobson, *U. of California, Los Angeles*
Kai Johnsson, *EPFL, Lausanne*
Peter Jonas, *Inst. of Science & Technology (IST) Austria*
Matt Kaeberlein, *U. of Washington*
William Kaelin Jr., *Dana-Farber Cancer Inst.*
Daniel Kahne, *Harvard U.*
Daniel Kammen, *U. of California, Berkeley*
Masashi Kawasaki, *U. of Tokyo*
Y. Narry Kim, *Seoul National U.*
Joel Kingsolver, *U. of North Carolina at Chapel Hill*
Robert Kingston, *Harvard Medical School*
Etienne Kochkin, *Ecole Normale Supérieure*
Alexander Kolodkin, *Johns Hopkins U.*
Alberto R. Kornblihtt, *U. of Buenos Aires*
Leonid Kruglyak, *UCIA*
Thomas Langer, *U. of Cologne*
Mitchell A. Lazar, *U. of Pennsylvania*
David Lazer, *Harvard U.*
Thomas Lecuit, *IGDM*
Virginia Lee, *U. of Pennsylvania*
Stanley Lemon, *U. of North Carolina at Chapel Hill*
Ottoline Leyner, *Cambridge U.*
Marcia C. Linn, *U. of California, Berkeley*
Jiangsu Liu, *Michigan State U.*
Luis Liz-Marzan, *ICIBiomaGUNE*
Jonathan Losos, *Harvard U.*
Ke Lu, *Chinese Acad. of Sciences*
Christian Lüscher, *U. of Geneva*
Laura Machesky, *GRUK Beatson Inst. for Cancer Research*
Anne Magurran, *U. of St. Andrews*
Oscar Marin, *CSIC U. Miguel Hernández*
Charles Marshall, *U. of California, Berkeley*
C. Robertson McClung, *Dartmouth College*
Graham Medley, *U. of Warwick*
Tom Misteli, *NCI*
Yasushi Miyashita, *U. of Tokyo*
Mary Ann Moran, *U. of Georgia*
Richard Morris, *U. of Edinburgh*
Alison Mousing-Reif, *NC State U. (\$)*
Sean Munro, *MRC Lab. of Molecular Biology*
Thomas Murray, *The Hastings Center*
James Neuman, *Stanford U. School of Med.*
Daniel Neuman, *U. of California, Berkeley*
Kitty Nymeyer, *U. of Twente*
Pär Nordlund, *Karolinska Inst.*
Helga Nowotny, *European Research Advisory Board*
Ben Oken, *MIT*
Joel Orenstein, *U. of California Berkeley & Lawrence Berkeley National Lab*
Harry Orr, *U. of Minnesota*
Andrew Oswald, *U. of Warwick*
Steve Palumbi, *Stanford U.*
Jane Parker, *Max Planck Inst. of Plant Breeding Research*
Giovanni Parmigiani, *Dana-Farber Cancer Inst. (\$)*
Donald R. Paul, *U. of Texas, Austin*
John H. J. Petrini, *Memorial Sloan Kettering Cancer Center*
Joshua Plotkin, *U. of Pennsylvania*
Albert Polman, *FOM Institute AMOLF*
Philippe Poulin, *CNRS*
Jonathan Pritchard, *Stanford U.*
David Randall, *Colorado State U.*
Colin Renfrew, *U. of Cambridge*
Felix Rey, *Institut Pasteur*
Trevor Robbins, *U. of Cambridge*
Jim Roberts, *Fred Hutchinson Cancer Research Ctr.*
Barbara A. Romanowicz, *U. of California, Berkeley*
Jens Rostrup-Nielsen, *Haldor Topsøe*
Mike Ryan, *U. of Texas, Austin*
Mitinori Saitou, *Kyoto U.*
Shimon Sakaguchi, *Kyoto U.*
Miquel Salmeron, *Lawrence Berkeley National Lab*
Jurgen Sankhithier, *Medical U. of Vienna*
Alexander Schier, *Harvard U.*
Randy Seeley, *U. of Cincinnati*
Vladimir Shalunov, *Pardee U.*
Robert Siliciano, *Johns Hopkins School of Medicine*
Dennis Simon, *Arizona State U.*
Alison Smith, *John Innes Centre*
Richard Smith, *U. of North Carolina (\$)*
John Speakman, *U. of Aberdeen*
Allan C. Spradling, *Carnegie Institution of Washington*
Jonathan Sprent, *Garvan Inst. of Medical Research*
Eric Steig, *U. of Washington*
Paula Stephan, *Georgia State U. and National Bureau of Economic Research*
Moly Stevens, *Imperial College London*
Alexander Schier, *Harvard U.*
Ira Tabas, *Columbia U.*
Sarah Teichmann, *Cambridge U.*
John Thomas, *North Carolina State U.*
Shubha Tole, *Institute of Fundamental Research*
Christopher Tyler-Smith, *The Wellcome Trust Sanger Inst.*
Herbert Virgin, *Washington U.*
Bert Vogelstein, *Johns Hopkins U.*
Christine Volok, *U. of Göttingen*
Douglas Wallace, *Dalhousie U.*
David Wallace, *Weizmann Inst. of Science*
Ian Wainman, *U. of Oxford*
Jane-Ling Wang, *U. of California, Davis*
David A. Warde, *Swedish U. of Agric. Sciences*
David Waxman, *Yale U.*
Jonathan Weissman, *U. of California, San Francisco*
Chris Winkle, *U. of Missouri (\$)*
Jan A. Wilson, *The Scripps Res. Inst. (\$)*
Timothy D. Wilson, *U. of Virginia*
Rosemary Wyse, *Johns Hopkins U.*
Jan Zaenlen, *Leiden U.*
Kenneth Zaret, *U. of Pennsylvania School of Medicine*
Jonathan Zehr, *U. of California, Santa Cruz*
Len Zhong, *Children's Hospital Boston*
Maria Zuber, *MIT*

BOOK REVIEW BOARD

David Bloom, *Harvard U.*, Samuel Bowring, *MIT*, Angela Creager, *Princeton U.*, Richard Sweder, *U. of Chicago*, Ed Wasserman, *DuPont*

This material was copied

The quest for a magic bullet

Widely used in science and medicine today, monoclonal antibodies got off to a rocky start

By Sudhakaran Prabhakaran

On a cold January evening in 1975, postdoctoral fellow Georges Köhler brought his wife to the lab to keep him company as he checked on his latest experiment. Far from the uneventful evening he anticipated, what he observed that night would transform the world of drug development and disease treatment. “I looked down at the first two plates. I saw these halos.... It was the best result I could think of,” he recalls. The halos were evidence that the cells in the petri dish were secreting highly specific antibodies. Dubbed “monoclonal antibodies,” or Mabs, they would have a radical influence on both science and medicine in the years that followed.

In her book, *The Lock and Key of Medicine*, Lara Marks presents a compelling, well-researched account of the discovery of Mabs and the development of Mab-based treatments and therapies. The book also narrates the challenges faced by César Milstein (Köhler’s postdoctoral adviser) and his collaborators, from patenting their findings to raising money for further testing and scaling up production. It is an excellent account of all the impediments the researchers faced in bringing Mabs from the bench to the market. Personal stories of the major players involved are skillfully interwoven with the narrative, bringing a human face to the drug discovery process.

In the early 1970s, Köhler and Milstein were studying the variable regions of antibodies—the proteins that recognize foreign molecules and tag them for destruction—with the hope of understanding how diverse populations of antibodies are generated by the mammalian immune system. In the course of their studies, they developed a technique that enabled the mass production of antibodies designed to recognize a specific antigen. The technique involved fusing a myeloma cell with an antibody-producing

B cell taken from the spleen of an immunized mouse. The B cell provided the immunological specificity, whereas the myeloma lent immortality to the construct.

These hybrid cells, or hybridomas as they were later called, became a vehicle for thousands of other biomedical inventions. However, the initial reception to this breakthrough was lukewarm. When they tried to publish their results, the editors at *Nature* reportedly requested that the article be shortened and did not feature it prominently in the journal, and their patent application was rejected.



César Milstein (left), Georges Köhler (right), and Niels Jerne (not pictured) were awarded the Nobel Prize in 1984 for their work on monoclonal antibodies.

Milstein sent samples and protocols of his newly created antibody-secreting cell lines to other research institutions and even trained scientists to generate their own hybridomas. One such scientist who benefited from this goodwill was Hilary Koprowski, director of the Wistar Institute in Philadelphia. The first patents for monoclonal antibodies were granted to Koprowski and his colleagues in October 1979 (for Mabs targeting influenza antigens) and April 1980 (for Mabs targeting tumor antigens). The “Wistar patents” proved controversial in the scientific community, because the antibodies had been created using the cell lines originally supplied by Milstein.

In the years that followed, there was an explosion in Mab research. Some were generated to identify different types of white blood cells, and several proved to be important in investigating HIV/AIDS. The first medical

The Lock and Key of Medicine Monoclonal Antibodies and the Transformation of Healthcare

Lara V. Marks

Yale University Press, 2015.

344 pp.



application of this technology used Mabs to purify interferons, signaling proteins that are released by cells in response to the presence of pathogens.

Mabs were soon being used to identify blood group types, an application that radically improved the accuracy and cost of blood typing. This now-routine test has since saved millions of lives.

After these initial success stories, many clinicians and founders of biotech companies began to believe that Mabs were “magic bullets” for diagnosing and curing diseases. In 1979, Koprowski cofounded Centocor, one of the original companies that exploited Mabs to diagnose cancer, cardiovascular disorders, and liver problems. The fortunes of Centocor ebbed and flowed during the 1980s and 1990s. It was acquired by Johnson & Johnson in 1999 and is known today as Janssen Biotech. It is one of the few original companies still in existence today.

In 1995, edrecolomab (Panorex)—a Mab developed in mice—was licensed by German authorities as an adjuvant therapy for post-operative colorectal cancer. It was the first Mab-based cancer therapeutic to proceed to market. In 1997, rituximab (Rituxan), a chimeric (part human and part mouse) Mab, was authorized by the FDA to treat B cell lymphoma. It was later found to be beneficial in the treatment of rheumatoid arthritis as well.

By 2012, there were more than 30 Mab drugs on the market, generating more than \$50 billion in revenue (10 of which generated profits exceeding \$1 billion each). The number of Mab-based therapies (and their market share) will likely increase with time.

Marks has done great justice to the topic, although the book would have been strengthened by the inclusion of additional illustrations and a broader discussion of the impact of Mabs on basic science. This book is in many ways a tribute to Köhler and Milstein, which makes the timing of its publication (just over 40 years since that fateful January evening) all the more appropriate.

10.1126/science.aac5603

The reviewer is at *Science Signaling*, AAAS, Washington, DC 20005, USA. E-mail: sprabaka@aaas.org

SCIENCE sciencemag.org