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Regulating emerging
technologies p. 384

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*Unlocking
the past*

Ancient DNA comes
of age p. 358

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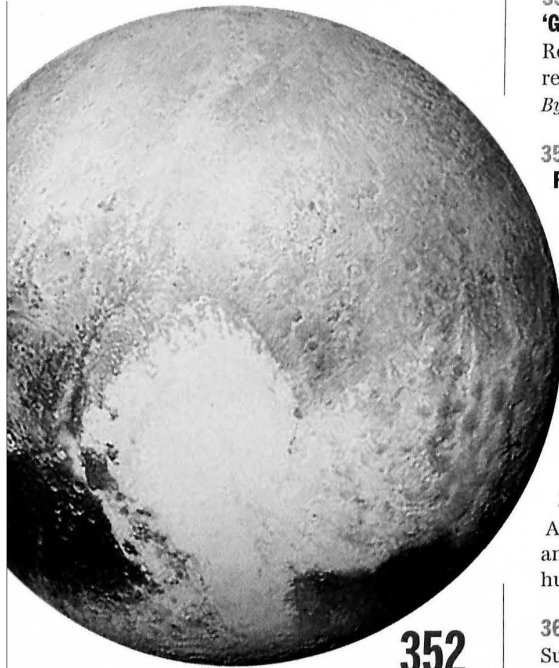
CONTENTS

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

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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

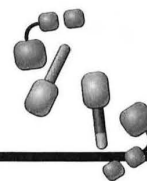
386 TOWARD AN HIV VACCINE: A SCIENTIFIC JOURNEY

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

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The quest for a magic bullet

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

By Sudhakaran Prabakaran

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

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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.

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