

The lingering legacy of
Deepwater Horizon pp. 11 & 22

The future of human
genome editing p. 36

Drilling into engine oil
antiwear films pp. 40 & 102

PR

RECEIVED

APR 15 2015

UNIVERSITY LIBRARY

\$10
3 APRIL 2015
sciencemag.org

Science

AAAS

SPECIAL ISSUE

Cancer Immunology and Immunotherapy

DO NOT REMOVE FROM
CURRENT PERIODICALS
ROOM

Genome & Co. v. Univ. of Chicago
PGR2019-00002
UNIV. CHICAGO EX. 2035

DOCKET
ALARM

Find authenticated court documents without watermarks at docketalarm.com.



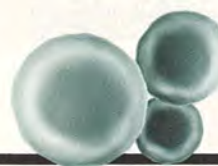
ONE
FOR
ALL

ALL
FOR
YOU

General Library System
University of Wisconsin - Madison
728 State Street
Madison, WI 53706-1494
U.S.A.

CONTENTS

3 APRIL 2015 • VOLUME 348 • ISSUE 6230



41 & 128

How cells dampen gene noise

NEWS

IN BRIEF

12 Roundup of the week's news

IN DEPTH

14 EGGS' POWER PLANTS ENERGIZE NEW IVF DEBATE

Firm adding energy-generating mitochondria to egg cells has already produced human pregnancies
By J. Couzin-Frankel

15 A CHILD-KILLING TOXIN EMERGES FROM SHADOWS

Scientists link mystery deaths in India to consumption of lychees
By P. Pulla

17 'THE BLOB' INVADES PACIFIC, FLUMMOXING CLIMATE EXPERTS

Persistent mass of warm water is reshuffling ocean currents, marine ecosystems, and inland weather
By E. Kintisch

18 HOAX-DETECTING SOFTWARE SPOTS FAKE PAPERS

Springer jumps into sham submissions arms race
By J. Bohannon



PHOTO (BOTTOM): © GERALD HERBERT/AP/CORBIS

20 AS EBOLA WANES, TRIALS JOCKEY FOR PATIENTS

Researchers debate ending some trials to allow others to go forward
By K. Kupferschmidt

FEATURES

22 DEEPWATER HORIZON: AFTER THE OIL

Five years on, the world's largest accidental marine spill has left subtle scars on the Gulf of Mexico
By W. Cornwall

27 Critics question plans to spray dispersant in future deep spills

By W. Cornwall
▶ EDITORIAL P. 11; BOOKS ET AL. P. 49; PODCAST



INSIGHTS

LETTERS

32 NEXTGEN VOICES

PERSPECTIVES

36 A PRUDENT PATH FORWARD FOR GENOMIC ENGINEERING AND GERMLINE GENE MODIFICATION

A framework for open discourse on the use of CRISPR-Cas9 technology to manipulate the human genome is urgently needed
By D. Baltimore et al.

38 DEFINING THE EPOCH WE LIVE IN

Is a formally designated "Anthropocene" a good idea?
By W. F. Ruddiman et al.

40 TRACKING ANTIWEAR FILM FORMATION

Atomic force microscopy visualizes the formation of a lubricating film
By U. D. Schwarz
▶ REPORT P. 102

41 MicroRNAs SILENCE THE NOISY GENOME

Evolution may have selected for a dampening service for genes whose noise may have otherwise been too high
By Y. Hoffman and Y. Pilpel
▶ REPORT P. 128

42 INFANTS EXPLORE THE UNEXPECTED

Infants are more likely to explore objects that behave in unexpected ways, such as passing through walls
By L. Schulz
▶ RESEARCH ARTICLE P. 91

44 HOW YOUNG STARS GROW AND BECOME FOCUSED

Observations 18 years apart capture early changes of a massive star
By M. G. Hoare
▶ REPORT P. 114

45 MULTIPLYING CANCER IMMUNITY

A soluble ligand of an innate immunoreceptor arms natural killers for tumor attack
By A. Steinle and A. Cerwenka
▶ REPORT P. 136; CANCER IMMUNOLOGY AND IMMUNOTHERAPY SECTION P. 54

46 EBOLA AND BEYOND

Recent experiences in confronting the Ebola epidemic suggest principles for vaccine efficacy trials in challenging environments
By M. Lipsitch et al.

BOOKS ET AL.

49 p53

By S. Armstrong, reviewed by A. Mandinova and S. W. Lee
▶ CANCER IMMUNOLOGY AND IMMUNOTHERAPY SECTION P. 54

49 A SEA IN FLAMES

By C. Safina
▶ EDITORIAL P. 11; NEWS STORY P. 22

51 CORNELIA PARKER

M. Griffiths, curator, reviewed by D. Dixon
▶ VIDEO

DEPARTMENTS

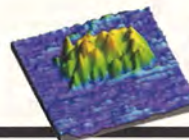
11 EDITORIAL

A community for disaster science
By Marcia McNutt
▶ NEWS STORY P. 22; BOOKS ET AL. P. 49; PODCAST

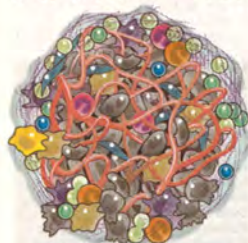
150 WORKING LIFE

A career is like a love affair
By Madeleine Jacobs

Science Staff 8
New Products 141
Science Careers 142



3 APRIL 2015 • VOLUME 348 • ISSUE 6230



SPECIAL SECTION

Cancer Immunology and Immunotherapy

INTRODUCTION

54 Realizing the promise

REVIEWS

56 The future of immune checkpoint therapy *P. Sharma and J. P. Allison*62 Adoptive cell transfer as personalized immunotherapy for human cancer *S. A. Rosenberg and N. P. Restifo*69 Neoantigens in cancer immunotherapy *T. N. Schumacher and R. D. Schreiber*74 T cell exclusion, immune privilege, and the tumor microenvironment *J. A. Joyce and D. T. Fearon*80 Cancer and the microbiota *W. S. Garrett*

ON THE COVER



Cancer immunotherapy harnesses the power of the immune system to kill tumors. These therapies aim to activate and expand T cells, such as those shown in blue, to specifically kill tumors (black). Current approaches

include antibodies targeting inhibitory proteins on T cells, adoptive T cell therapy, and tumor vaccines, among others. See page 54.

Illustration: *Valerie Altounian/Science*

SEE ALSO ▶ PERSPECTIVE P. 45 ▶ BOOKS ET AL. P. 49 ▶ REPORTS PP. 124 & 136 ▶ REPORT BY B. M. CARRENO ET AL. 10.1126/science.aaa3828
▶ SCIENCE CAREERS STORY BY R. BERNSTEIN

RESEARCH

IN BRIEF

87 From *Science* and other journals

RESEARCH ARTICLES

90 EPIGENETICS

Epigenetic inheritance uncoupled from sequence-specific recruitment *K. Raganathan et al.*

RESEARCH ARTICLE SUMMARY; FOR FULL TEXT:

dx.doi.org/10.1126/science.1258699

▶ REPORT P. 132

91 COGNITIVE DEVELOPMENT

Observing the unexpected enhances infants' learning and exploration *A. E. Stahl and L. Feigenson*

▶ PERSPECTIVE P. 42

95 RIBOSOME

The structure of the human mitochondrial ribosome *A. Amunts et al.*

▶ RESEARCH ARTICLE BY B. J. GREBER ET AL.

10.1126/science.aaa3872

REPORTS

99 MOLECULAR PHYSICS

Production of trilobite Rydberg molecule dimers with kilo-Debye permanent electric dipole moments *D. Booth et al.*

102 TRIBOLOGY

Mechanisms of antiwear tribofilm growth revealed in situ by single-asperity sliding contacts *N. N. Gosvami et al.*

▶ PERSPECTIVE P. 40

106 FRUSTRATED MAGNETISM

Large thermal Hall conductivity of neutral spin excitations in a frustrated quantum magnet *M. Hirschberger et al.*

109 THERMOELECTRICS

Dense dislocation arrays embedded in grain boundaries for high-performance bulk thermoelectrics *S. I. Kim et al.*

114 STELLAR PHYSICS

Observing the onset of outflow collimation in a massive protostar *C. Carrasco-González et al.*

▶ PERSPECTIVE P. 44

117 VIROLOGY

Mutation rate and genotype variation of Ebola virus from Mali case sequences *T. Hoenen et al.*

120 PLANT BIOLOGY

Suppression of endogenous gene silencing by bidirectional cytoplasmic RNA decay in *Arabidopsis* *X. Zhang et al.*

124 CANCER IMMUNOLOGY

Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer *N. A. Rizvi et al.*

▶ CANCER IMMUNOLOGY AND IMMUNOTHERAPY SECTION P. 54

128 GENE EXPRESSION

MicroRNA control of protein expression noise *J. M. Schmiedel et al.*

▶ PERSPECTIVE P. 41

132 EPIGENETICS

Restricted epigenetic inheritance of H3K9 methylation *P. N. C. B. Audergon et al.*

▶ RESEARCH ARTICLE P. 90

136 ANTITUMOR IMMUNITY

A shed NKG2D ligand that promotes natural killer cell activation and tumor rejection *W. Deng et al.*

▶ PERSPECTIVE P. 45; CANCER IMMUNOLOGY AND IMMUNOTHERAPY SECTION P. 54

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 #1254 88122. Publications Mail Agreement Number 1069624. Printed in the U.S.A. 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 \$30.00 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.

REVIEWS

The future of immune checkpoint therapy

Padmanee Sharma^{1,2*} and James P. Allison^{1*}

Immune checkpoint therapy, which targets regulatory pathways in T cells to enhance antitumor immune responses, has led to important clinical advances and provided a new weapon against cancer. This therapy has elicited durable clinical responses and, in a fraction of patients, long-term remissions where patients exhibit no clinical signs of cancer for many years. The way forward for this class of novel agents lies in our ability to understand human immune responses in the tumor microenvironment. This will provide valuable information regarding the dynamic nature of the immune response and regulation of additional pathways that will need to be targeted through combination therapies to provide survival benefit for greater numbers of patients.

The field of immune checkpoint therapy has joined the ranks of surgery, radiation, chemotherapy, and targeted therapy as a pillar of cancer therapy. Three new immune checkpoint agents have now been approved by the U.S. Food and Drug Administration (FDA) for the treatment of melanoma, and there is a high expectation that these agents, and others in this class, will also be approved over the next several years for treatment of patients with lung cancer, kidney cancer, bladder cancer, prostate cancer, lymphoma, and many other tumor types. The antibody against CTLA-4 ipilimumab was approved in 2011, and two antibodies against PD-1 (pembrolizumab and nivolumab) were approved in 2014. These drugs represent a radical and disruptive change in cancer therapy in two ways. First, they do not target the tumor cell, but target molecules involved in regulation of T cells, the soldiers

of the immune system. And, perhaps in a more radical shift, the goal of the therapy is not to activate the immune system to attack particular targets on tumor cells, but rather to remove inhibitory pathways that block effective antitumor T cell responses. Immune checkpoint therapy, with anti-CTLA-4 having longer follow-up than other agents, leads to durable clinical responses that can last a decade and more, but only in a fraction of patients. There are ongoing studies to identify predictive biomarkers with which to select patients for treatment with a particular agent, but the complexity of the immune response has made this difficult.

¹Department of Immunology, M.D. Anderson Cancer Center, Houston, TX, USA. ²Genitourinary Medical Oncology, M.D. Anderson Cancer Center, Houston, TX, USA.
*Corresponding author. E-mail: padsharma@mdanderson.org (P.S.); jallison@mdanderson.org (J.P.A.)

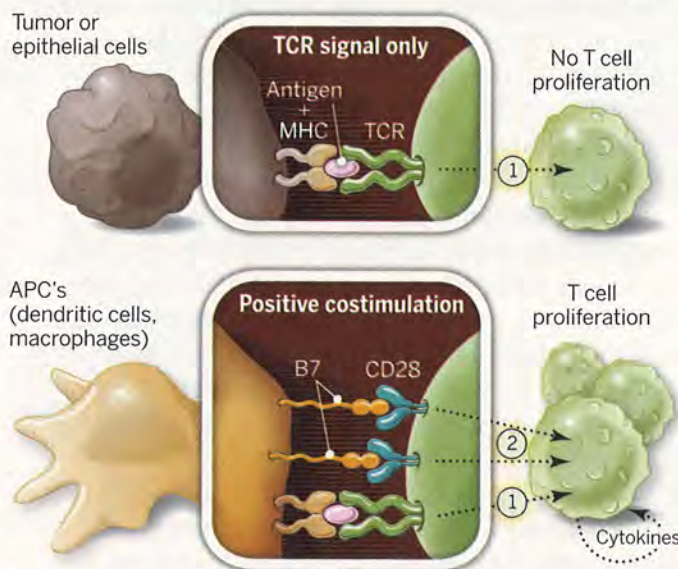


Fig. 1. Activation of T cells requires two signals. T cell activation occurs only after interaction between T cell receptor (TCR) and antigen in the context of MHC (signal 1) plus CD28 costimulation (signal 2).

In the past two decades, remarkable advances in basic science have led to new strategies for the treatment of cancer, which are justifiably generating optimism that it may soon be possible to cure a subset of patients with some types of cancer. We now have detailed knowledge of the molecular basis of cancer to allow a more “personalized” treatment based on genomic sequencing of an individual’s cancer cells to identify specific mutations in genes. These mutations can then be targeted with compounds to block the downstream pathways that drive cancer development and progression. Therefore, each specific mutation serves as the predictive biomarker for selecting patients for treatment with a given agent. For example, patients with melanoma whose tumors harbor the BRAFV600E mutation, which enables constitutive activation of the BRAF signaling pathway, would be selected to receive treatment with an agent

that inhibits BRAF (1, 2). These targeted therapies have led to promising clinical responses, albeit generally of short duration, in patients whose tumors express the appropriate target biomarker.

The clinical success of genomically targeted agents laid the foundation for other cancer therapies, including the prerequisite to identify predictive biomarkers for selection of patients for treatment. Eventually, as the field of cancer immunotherapy found clinical success with agents based on a greater understanding of how to unleash T cell responses by targeting immune checkpoints, it became clear that the framework used for identification of predictive biomarkers for genomically targeted agents would present a challenge. As opposed to mutated genes in tumors that permanently mark a tumor, the immune response is dynamic and changes rapidly. Therefore, the issue facing the field of cancer immunotherapy may not be the identification of a single biomarker to select a subset of patients for treatment. Instead, we must assess the effectiveness of an evolving immune response, define the immune response that contributes to clinical benefit, and then, hopefully, drive every patient’s immune response in that direction through combination therapies.

Tumor microenvironment: Cancer cells and host immune responses

Tumors are composed of many cell types, including the cell of origin with genetic alterations and a myriad of other cells, such as fibroblasts, endothelial cells, and eventually, perhaps, a variety of immune cells. Initially the immune infiltrate may be scarce, but eventually may contain natural killer (NK) cells and macrophages with lytic capacity and, perhaps most importantly, T cells. T cells attack tumor cells that express tumor-specific antigens in the form of complexes of tumor-derived peptides bound to major histocompatibility complex (MHC) molecules on the cell. The tumor antigens can be derived from oncogenic viruses, differentiation antigens, epigenetically regulated molecules such as cancer testis antigens, or neoantigens derived from mutations associated with the process of carcinogenesis (3). T cells survey the microenvironment and become activated when tumor antigens are recognized. They then proliferate and differentiate, ultimately leading to the T cell’s ability to attack and destroy cells that express relevant antigens. However, regulation of T cell responses is an extremely complex process consisting of both stimulatory and inhibitory cell intrinsic signaling pathways, which limit T cell responses against cancer and prevent eradication of tumors.

Recognition of antigen-MHC complexes by the T cell antigen receptor is not sufficient for

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.