CONTENTS

1030 & 1061
Reflections on water splitting

27 NOVEMBER 2015 • VOLUME 350 • ISSUE 6264

FEATURES

ON THE COVER

Symbolizing the choices facing climate negotiators next week in Paris, a windmill and the smokestack of a coal-burning power plant stand less than a kilometer apart in a coal-mining area of North Rhine-Westphalia, Germany. See pages 1007, 1016, and 1034. *Photo: © Jochen Tack/imageBROKER/Corbis*

SEE ALSO ▸ EDITORIAL P. 1007 ▸ PERSPECTIVE P. 1034 ▸ POLICY FORUM BY A. A. FAWCETT *ET AL.* 10.1126/science.aad5761

NEWS

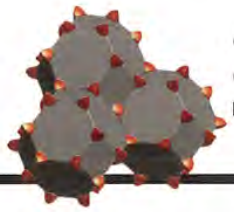
IN BRIEF

IN DEPTH

INSIGHTS

PERSPECTIVES

1038 & 1077
Cichlid extinction



1069
Flow paths through salt

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.

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.

Science
AAAS
1200 New York Avenue, NW, Washington, DC 20005
Bateman House, 82-88 Hills Road, Cambridge, UK CB2 1LQ

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

Nationale de la Recherche. A.S. was supported by BMSI YIG 2014. F.G. is supported by SIgN core funding. L.Z., M.C., and I.B.G. are all sponsored by Association pour la Recherche contre le Cancer (PGA120140200851). F.C. was supported by INCA-DGOS (GOLD H78008). N.C. was supported by INCA-DGOS (GOLD study; 2012-1-RT-14-IGR-01). L'Oreal awarded a prize to M.V. We are grateful to the staff of the animal facility of Gustave Roussy and Institut Pasteur. We thank P. Gonin, B. Ryffel, T. Angelique, N. Chanthapathet, H. Li, and S. Zuberogoitia for technical help. DNA sequence reads from this study have been submitted to the NCBI under the Bioproject IDPRJNA299112 and are available from the Sequence Read Archive (SRP Study accession SRP065109; run accession numbers SRR2758006, SRR2758031, SRR2758178, SRR2758179, SRR2758180, SRR2758181, SRR2768454, and SRR2768457.

SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/350/6264/1079/suppl/DC1
Materials and Methods
Figs. S1 to S22
Tables S1 to S5
References (*19*–*35*)

3 April 2015; accepted 21 October 2015
Published online 5 November 2015;
10.1126/science.aad1329

CANCER IMMUNOTHERAPY

Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy

Ayelet Sivan,[1*] Leticia Corrales,[1*] Nathaniel Hubert,[2] Jason B. Williams,[1] Keston Aquino-Michaels,[3] Zachary M. Earley,[2] Franco W. Benyamin,[1] Yuk Man Lei,[2] Bana Jabri,[2] Maria-Luisa Alegre,[2] Eugene B. Chang,[2] Thomas F. Gajewski[1,2†]

T cell infiltration of solid tumors is associated with favorable patient outcomes, yet the mechanisms underlying variable immune responses between individuals are not well understood. One possible modulator could be the intestinal microbiota. We compared melanoma growth in mice harboring distinct commensal microbiota and observed differences in spontaneous antitumor immunity, which were eliminated upon cohousing or after fecal transfer. Sequencing of the 16*S* ribosomal RNA identified *Bifidobacterium* as associated with the antitumor effects. Oral administration of *Bifidobacterium* alone improved tumor control to the same degree as programmed cell death protein 1 ligand 1 (PD-L1)–specific antibody therapy (checkpoint blockade), and combination treatment nearly abolished tumor outgrowth. Augmented dendritic cell function leading to enhanced CD8$^+$ T cell priming and accumulation in the tumor microenvironment mediated the effect. Our data suggest that manipulating the microbiota may modulate cancer immunotherapy.

Harnessing the host immune system constitutes a promising cancer therapeutic because of its potential to specifically target tumor cells although limiting harm to normal tissue. Enthusiasm has been fueled by recent clinical success, particularly with antibodies that block immune inhibitory pathways, specifically CTLA-4 and the axis between programmed cell death protein 1 (PD-1) and its ligand 1 (PD-L1) (*1*, *2*). Clinical responses to these immunotherapies are more frequent in patients who show evidence of an endogenous T cell response ongoing in the tumor microenvironment before therapy (*3*–*6*). However, the mechanisms that govern the presence or absence of this phenotype are not well understood. Theoretical sources of interpatient heterogeneity include host germline genetic differences, variability in patterns of somatic alterations in tumor cells, and environmental differences.

The gut microbiota plays an important role in shaping systemic immune responses (*7*–*9*). In the cancer context, a role for intestinal microbiota in mediating immune activation in response to chemotherapeutic agents has been demonstrated (*10*, *11*). However, it is not known whether commensal microbiota influence spontaneous immune responses against tumors and thereby affect the therapeutic activity of immunotherapeutic interventions, such as anti–PD-1/PD-L1 monoclonal antibodies (mAbs).

To address this question, we compared subcutaneous B16.SIY melanoma growth in genetically similar C57BL/6 mice derived from two different mouse facilities, Jackson Laboratory (JAX) and Taconic Farms (TAC), which have been shown to differ in their commensal microbes (*12*). We found that JAX and TAC mice exhibited significant differences in B16.SIY melanoma growth rate, with tumors growing more aggressively in TAC mice (Fig. 1A). This difference was immune-mediated: Tumor-specific T cell responses (Fig. 1, B and C) and intratumoral CD8$^+$ T cell accumulation (Fig. 1D) were significantly higher in JAX than in TAC mice. To begin to address whether this difference could be mediated by commensal microbiota, we cohoused JAX and TAC mice before tumor implantation. We found that cohousing ablated the differences in tumor growth (Fig. 1E) and immune responses (Fig. 1, F to H) between the two mouse populations, which suggested an environmental influence. Cohoused TAC and JAX mice appeared to acquire the JAX phenotype, which suggested that JAX mice may be colonized by commensal microbes that dominantly facilitate antitumor immunity.

To directly test the role of commensal bacteria in regulating antitumor immunity, we transferred JAX or TAC fecal suspensions into TAC and JAX recipients by oral gavage before tumor implantation (fig. S1A). We found that prophylactic transfer of JAX fecal material, but not saline or TAC fecal material, into TAC recipients was sufficient to delay tumor growth (Fig. 2A) and to enhance induction and infiltration of tumor-specific CD8$^+$ T cells (Fig. 2, B and C, and fig. S1B), which supported a microbe-derived effect. Reciprocal transfer of TAC fecal material into JAX recipients had a minimal effect on tumor growth rate and antitumor T cell responses (Fig. 2, A to C, and fig. S1B), consistent with the JAX-dominant effects observed upon cohousing.

To test whether manipulation of the microbial community could be effective as a therapy, we administered JAX fecal material alone or in combination with antibodies targeting PD-L1 (αPD-L1) to TAC mice bearing established tumors. Transfer of JAX fecal material alone resulted in significantly slower tumor growth (Fig. 2D), accompanied by increased tumor-specific T cell responses (Fig. 2E) and infiltration of antigen-specific T cells into the tumor (Fig. 2F), to the same degree as treatment with systemic αPD-L1 mAb. Combination treatment with both JAX fecal transfer and αPD-L1 mAb improved tumor control (Fig. 2D) and circulating tumor antigen–specific T cell responses (Fig. 2E), although there was little additive effect on accumulation of activated T cells within the tumor microenvironment (Fig. 2F). Consistent with these results, αPD-L1 therapy alone was significantly more efficacious in JAX mice compared with TAC mice (Fig. 2G), which paralleled improved antitumor T cell responses (fig. S1C). These data indicate that the commensal microbial composition can influence spontaneous antitumor immunity, as well as a response to immunotherapy with αPD-L1 mAb.

To identify specific bacteria associated with improved antitumor immune responses, we monitored the fecal bacterial content over time of mice that were subjected to administration of fecal permutations, using the 16*S* ribosomal RNA (rRNA) miSeq Illumina platform. Principal coordinate analysis revealed that fecal samples analyzed from TAC mice that received JAX fecal material gradually separated from samples obtained from sham- and TAC feces–inoculated TAC mice over time ($P = 0.001$ and $P = 0.003$, respectively, ANOSIM multivariate data analysis) and became similar

[1]Department of Pathology, University of Chicago, Chicago, IL 60637, USA. [2]Department of Medicine, University of Chicago, Chicago, IL 60637, USA. [3]Section of Genetic Medicine, University of Chicago, Chicago, IL 60637, USA.
*These authors contributed equally to this work. †Corresponding author. E-mail: tgajewsk@medicine.bsd.uchicago.edu

DOCKET ALARM

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.