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*The newsmakers of the year* **PAGE 437**

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# CONTENTS

22/29 December 2011 / Vol 480 / Issue No 7378

## 2011 IN REVIEW

### EDITORIAL

- 414 **Ten for 2011**  
Capturing the characters of the year

### NEWS

- 426 **2011 in review**  
From scandals to fallout and all points between
- 430 **Images of the year**

### FEATURES

- 437 **Nature's 10**  
Who were the people who made a mark on the past 12 months?



Cover and illustrations by Carl DeTorres

### COMMENT

- 447 **The new history**  
*Philip Ball*  
The major events of 2011 were driven by complexity as well as social media and globalization

### NEWS & VIEWS

- 468 **Editors' choice**  
A look back at some of the highlights from this year's News & Views

 [nature.com/2011](http://nature.com/2011)

## THIS WEEK

### EDITORIALS

- 413 **POLICY**  
**The morning after**  
The US government was wrong to overrule recommendations on Plan B
- 413 **ENVIRONMENT**  
**Defend the Amazon**  
Brazil's attempts to reform forest protection must be reworked

### WORLD VIEW

- 415 **Particle physics is at a turning point**  
*Gordon Kane*  
The putative discovery of the Higgs boson is a boon for string theorists

### RESEARCH HIGHLIGHTS

- 416 **SELECTIONS FROM THE SCIENTIFIC LITERATURE**



Mercury's magnetosphere / Egg counts / Bacterial microtubules / Why frogs make music / Lost *Hox* genes / Owning the world / Neanderthals not up to sniff

### SEVEN DAYS

- 418 **THE NEWS IN BRIEF**  
Fukushima finally in shutdown / The world's tiniest tetrapod / Vote on

## NEWS IN FOCUS

- 421 **BIOSAFETY**  
Altered bird-flu virus raises questions about lab security
- 423 **POLICY**  
US budget paves the way for new NIH centre



424 **ANIMAL RESEARCH**  
Report spells out tough criteria for NIH-funded chimp research

425 **POLICY**  
US integrity rules edge closer to reality

## CAREERS

- 575 **AWARDS**  
**Conscientious counsellors**  
*Nature's* 2011 mentoring awards go Parisienne
- 576 **COLUMN**  
**Testing the waters**  
Postdocs and industry do mix, say Christopher Tsang and Michael Fisher

**nature events**

Your guide to global scientific events

## COMMENT

- 449 **SCIENCE PUBLISHING**  
**The paper is not sacred**  
*Adam Marcus & Ivan Oranski*  
The rise in retractions this year argues for the broadening of peer review

### BOOKS & ARTS

- 451 **TECHNOLOGY**  
**Rise of the e-book**  
*Carl Zimmer*
- 452 **FOOD SCIENCE**  
**With pipette and ladle**  
*Harold McGee*
- 453 **Q&A**  
**The snowflake designer**  
Physicist Kenneth Libbrecht takes the study of snowflakes to extremes
- 455 **IN RETROSPECT**  
**On the Six-Cornered Snowflake**  
*Philip Ball*

### CORRESPONDENCE

- 457 Leonardo da Vinci's physics / Europe's threatened vultures / The first cells

### OBITUARY

- 458 **Lynn Margulis (1938–2011)**  
*James A Lake*

### FUTURES



# CONTENTS

22/29 December 2011 / Vol 480 / Issue No 7378

## RESEARCH

### NEW ONLINE

459 Papers published this week at nature.com

### NEWS & VIEWS

#### 460 PLANETARY SCIENCE

##### The ultimate fate of planets

Discovery of a planetary system in orbit around an evolved star

Eliza M R Kempton **SEE LETTER P.496**

#### 461 ECOLOGY

##### Bleak future for amphibians

Predicting the distribution of threats to amphibians

Ross A Alford **SEE LETTER P.516**

### MATERIALS SCIENCE

## Take charge

Repackaging organic semiconductors to be more flexible. **PAGE 504**



#### 463 ATOMIC PHYSICS

##### When ultracold is not cold enough

How to cool quantum atomic gases in optical lattices

Gretchen K Campbell **SEE LETTER P.500**

#### 463 PSYCHOLOGY

##### Who needs a leader?

The dynamics of joint improvisation

Sadaf Shadan

#### 465 CONDENSED-MATTER PHYSICS

##### A fresh twist on shrinking materials

Negative thermal expansion in scandium trifluoride

J Paul Attfield

#### 466 PHYSIOLOGY

##### On time metabolism

Glucocorticoid signalling by the clock

Joseph Bass **SEE LETTER P.552**

### REVIEWS

#### 471 ORGANIC CHEMISTRY Rethinking amide bond synthesis

V R Pattabiraman & J W Bode

#### 480 CANCER Cancer immunotherapy comes of age

I Mellman, G Coukos & G Dranoff

### ARTICLE

#### 490 GENOMICS DNA-binding factors shape the mouse methylome at distal regulatory regions

M B Stadler et al.

### LETTERS

#### 496 ASTRONOMY A compact system of small planets around a former red-giant star

S Charpinet et al. **SEE N&V P.460**

#### 500 PHYSICS Orbital excitation blockade and algorithmic cooling in quantum gases

W S Bakr et al. **SEE N&V P.463**

#### 504 MATERIALS SCIENCE Tuning charge transport in solution-sheared organic semiconductors using lattice strain

G Giri et al.

#### 509 CLIMATE SCIENCE Forcing of wet phases in southeast Africa over the past 17,000 years

E Schefuß, H Kuhlmann, G Mollenhauer, M Prange & J Pätzold

#### 513 PALAEOONTOLOGY Lowland-upland migration of sauropod dinosaurs during the Late Jurassic epoch

H C Fricke, J Henceroth & M E Hoerner

#### 516 ECOLOGY Additive threats from pathogens, climate and land-use change for global amphibian diversity

C Hof, M B Araújo, W Jetz & C Rahbek **SEE N&V P.461**

#### 520 GENOMICS The *Medicago* genome provides insight into the evolution of rhizobial symbioses

N D Young et al.

#### 525 NEUROBIOLOGY Natural polymorphisms in *C. elegans* HECW-1 E3 ligase affect pathogen avoidance behaviour

H C Chang, J Paek & D H Kim

#### 530 VIROLOGY Adherens junction protein nectin-4 is the epithelial receptor for

#### 534 PARASITOLOGY Basigin is a receptor essential for erythrocyte invasion by *Plasmodium falciparum*

C Crosnier et al.

#### 538 IMMUNOLOGY Response to self antigen imprints regulatory memory in tissues

M D Rosenblum et al.

#### 543 CELL BIOLOGY Excitation-induced ataxin-3 aggregation in neurons from patients with Machado-Joseph disease

P Koch et al.

#### 547 STEM CELLS Dopamine neurons derived from human ES cells efficiently engraft in animal models of Parkinson's disease

S Kriks et al.

#### 552 METABOLISM Cryptochromes mediate rhythmic repression of the glucocorticoid receptor

K A Lamia et al. **SEE N&V P.466**

#### 557 BIOCHEMISTRY GlcNAcylation of histone H2B facilitates its monoubiquitination

R Fujiki et al.

#### 561 MOLECULAR BIOLOGY An equilibrium-dependent retroviral mRNA switch regulates translational recoding

B Houck-Loomis et al.

#### 565 STRUCTURAL BIOLOGY Structures of the multidrug exporter AcrB reveal a proximal multisite drug-binding pocket

R Nakashima, K Sakurai, S Yamasaki, K Nishino & A Yamaguchi

#### 570 BIOCHEMISTRY Intermediates in the transformation of phosphonates to phosphate by bacteria

S S Kamat, H J Williams & F M Raushel

### GENOMICS

## Top model

The genome of barrel clover, green manure and model legume. **PAGE 520**





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## REVIEW

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## Cancer immunotherapy comes of age

Ira Mellman<sup>1</sup>, George Coukos<sup>2</sup> & Glenn Dranoff<sup>3</sup>

Activating the immune system for therapeutic benefit in cancer has long been a goal in immunology and oncology. After decades of disappointment, the tide has finally changed due to the success of recent proof-of-concept clinical trials. Most notable has been the ability of the anti-CTLA4 antibody, ipilimumab, to achieve a significant increase in survival for patients with metastatic melanoma, for which conventional therapies have failed. In the context of advances in the understanding of how tolerance, immunity and immunosuppression regulate antitumour immune responses together with the advent of targeted therapies, these successes suggest that active immunotherapy represents a path to obtain a durable and long-lasting response in cancer patients.

The passive transfer of anticancer monoclonal antibodies and donor T cells in the context of allogeneic bone marrow transplantation are effective treatments for a variety of haematological and solid malignancies<sup>1</sup>. Although not always thought of as 'immunotherapy', the success of these biotherapeutics probably reflects the ability of the donor cells or antibodies to induce an immediate immune reaction against the cancer, bypassing the requirement to activate endogenous immunity. These immune treatments have been well-established in oncology for several decades, and continued advances in antibody and T-cell engineering should further enhance their clinical impact in the years to come (Box 1).

In contrast to these passive immunotherapy strategies, the active stimulation of specific and durable antitumour immunity has proved elusive. In 1891, William Coley, a young New York surgeon, began intratumoural injections of live or inactivated *Streptococcus pyogenes* and *Serratia marcescens* in an effort to reproduce the spontaneous remissions of sarcomas observed in rare-cancer patients who had developed erysipelas<sup>2</sup>. Given Elie Metchnikoff's contemporaneous work demonstrating the immune system's ability to cause inflammation and destroy invading bacteria, 'Coley's toxins' made sense by acting to stimulate antibacterial phagocytes that might kill bystander tumour cells. Some significant responses were recorded over the ensuing 40 years, but successes were sporadic, difficult to reproduce and not obtained in a scientifically rigorous fashion. Superficial bladder cancer was one notable exception, for which the intravesical injection of live bacillus Calmette-Guérin after surgical resection was shown to prolong patient survival<sup>3</sup>. Other than this particular clinical setting, the approach was never embraced by oncologists who continued to rely on surgery and, increasingly, on effective new methods, such as radiation therapy and ultimately chemotherapy. Coley's strategy was further discounted due to the very real risks associated with the administration of infectious, or at least pyrogenic, agents to already weakened cancer patients; this is ironic given the trauma associated with the treatments that did come into common use. Thus began the history of cancer immunotherapy. Before continuing, however, it is useful to summarize what must happen to elicit a protective immune response to cancer, and why overcoming these barriers has been so difficult.

### Generating anticancer immunity is a multistep challenge

Based on our current understanding of the immune response, there are three distinct steps that must be achieved, either spontaneously or therapeutically, to mount effective antitumour immunity (Fig. 1). To

#### BOX 1

### Established immune treatments

Nine monoclonal antibodies targeting six cancer-associated proteins (Her2/neu, EGFR, VEGF, CD20, CD52 and CD33) are approved for the treatment of solid and haematological malignancies. In addition to antagonizing oncogenic pathways, these biotherapeutics may act by opsonizing tumour cells and triggering their death or removal by antibody-dependent cellular cytotoxicity or phagocytosis<sup>94</sup>. Ongoing investigations in murine models and patients raise the possibility that they may also stimulate adaptive immune responses in some settings<sup>95</sup>. Recently, the successful conjugation of toxins to antibodies has been achieved, and these have induced a clinical response in patients who are refractory to the naked antibody<sup>96</sup>. The concurrent administration of immunostimulatory cytokines such as IL-2 and GM-CSF may also enhance the efficacy of antibody therapy.

Allogeneic bone marrow transplantation and the infusion of donor lymphocytes can be a highly effective therapy for some leukaemias and lymphomas<sup>24</sup>. The graft-versus-leukaemia effects involve the direct killing of tumour cells by donor lymphocytes, together with the subsequent induction of broader innate and adaptive reactions. On the basis of these clinical benefits, many groups are exploring the use of adoptive T-cell therapy in the autologous setting. Promising strategies include the use of lymphodepletion before T-cell infusion, and the engineering of new T-cell specificities with CARs<sup>97</sup>.

Other immune treatments that have received the FDA approval include recombinant cytokines, such as IL-2 (Proleukin), which is used for melanoma and renal cell cancer. Response rates are low (~15%) and the significant risk of serious systemic inflammation requires administration as an in-patient. Interferon- $\alpha$  is another agent that gained approval for 'immunological cancers' (that is, melanoma or renal cell cancer). Although also associated with low response rates and high-dose toxicity, a small subset of melanoma patients, who are also predisposed to autoimmunity, has been shown to exhibit an impressive survival response<sup>98</sup>. It has been, however, difficult to pre-identify these patients, which limits the use of the approach. Yet, when seen, responses are durable, suggesting they reflect active antitumour immunity.

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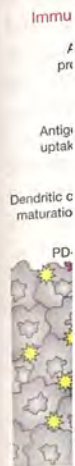


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