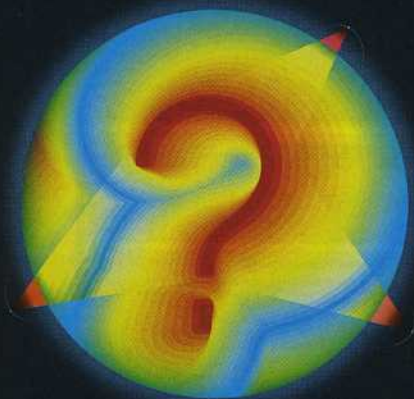


CONTENTS

19 September 2013 / Vol 501 / Issue No 7467

OUTLOOK FOR EARTH



Cover by Carl De Torres.

EDITORIAL

- 281 The final assessment**
The IPCC should change the way it issues climate reports

FEATURES

- 297 Outlook for Earth**
Striking a balance between uncertainty and the need for action
- 298 25 years of the IPCC**
A history of the planet's climate watchdog
- 300 Rising tide**
The struggle to predict the effects of climate change on the oceans

- 303 The climate chairman**
How Ottmar Edenhofer attains consensus among the experts in the IPCC

COMMENT

- 307 A patchwork of emissions cuts**
Elliot Diring
A nation-by-nation approach could work for climate mitigation
- 310 Pushing the climate frontier**
K John Holmes
We can still learn from nineteenth-century environmental surveys

 nature.com/IPCC2013

THIS WEEK

EDITORIALS

- 282 CRYPTOGRAPHY**
Spooked
Public trust in the Internet's security cannot be allowed to falter
- 282 LITERATURE**
Book smart
The art of story-telling — with added science

WORLD VIEW

- 283 The Himalayas must be protected**
Maharaj K Pandit
An international network is needed to monitor this fragile ecosystem

RESEARCH HIGHLIGHTS

- 284 SELECTIONS FROM THE SCIENTIFIC LITERATURE**
Graphene photodetectors shine / Variation in amyloids / Salamanders infected / Fruit cuts diabetes risk / Fossils record volcanism

SEVEN DAYS

- 286 THE NEWS IN BRIEF**
Voyager 1 reaches interstellar space / Australia does away with science minister / Massive water resources found in Kenya / Meningitis vaccine proves successful

NEWS IN FOCUS

- 289 POLICY**
German scientists prepare for election outcome
- 291 AGRICULTURE**
Plant breeders create grass that limits nitrogen emissions
- 292 ASTRONOMY**
Telescope strike stirs worker unrest in Chile
- 293 FUNDING**
Israel rejects Horizon 2020 rules
- 294 VIROLOGY**
Scientists lament lack of data on MERS coronavirus



CAREERS

- 449 LAB LIFE**
Battle zone
Personal differences are inevitable but there are ways of limiting the fallout
- 451 CAREER BRIEFS**

NATUREJOBS ADVERTISING FEATURE
Spotlight on postdoctoral positions

COMMENT

BOOKS & ARTS

- 312 FICTION**
Silicon and surveillance
Sean Carroll
- 313 INNOVATION**
Superpowered invention
Leonid Gokhberg & Dirk Meissner
- 314 MATHEMATICS**
Master puzzler
David Singmaster

CORRESPONDENCE

- 316 Ecuador's forests under siege / Restrict antimicrobials in food production / E-learning helps the poor / Italian impasse**



FUTURES
454 Reach for the stars
Priya Chand

CONTENTS

19 September 2013 / Vol 501 / Issue No 7467

RESEARCH

NEW ONLINE

317 Papers published this week at nature.com

NEWS & VIEWS

318 CLIMATE SCIENCE

The cause of the pause

An explanation for the recent hiatus in global warming

Isaac M Held **SEE LETTER P.403**

319 DEVELOPMENTAL NEUROSCIENCE

Miniature human brains

Generation of cerebral organoids from human iPS cells

Oliver Brüstle **SEE ARTICLE P.373**

321 OCEANOGRAPHY

Mountain waves in the deep ocean

Internal lee waves and deep-ocean mixing

Jennifer MacKinnon

322 PARASITOLOGY

Molecular one-upmanship

Mechanisms of immune resistance in *Trypanosoma brucei gambiense*

Jayne Raper & David J Friedman

SEE LETTER P.430

323 MATERIALS SCIENCE

Fast-track solar cells

Perovskite-containing solar cells break the 15% efficiency barrier

Michael D McGehee **SEE LETTER P.395**

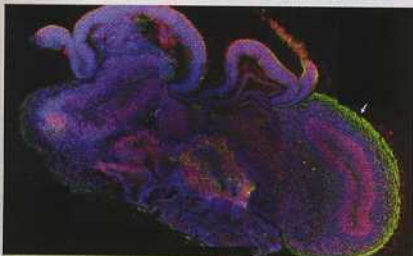
325 STEM CELLS

Down's syndrome link to ageing

Role of the deubiquitinating enzyme Usp16 in stem-cell self-renewal

George P Souroullas & Norman E Sharpless

SEE ARTICLE P.380



DEVELOPMENTAL NEUROSCIENCE

Brain work

Using patient-derived stem cells to create a brain-like organoid. **PAGE 373**



NANOPARTICLES

Good as gold

Silver nanoclusters can rival gold for stability — and usefulness. **PAGE 399**

ARTICLES

373 **NEUROGENESIS** Cerebral organoids model human brain development and microcephaly

M A Lancaster et al. **SEE N&V P.319**

380 **STEM CELLS** Usp16 contributes to somatic stem-cell defects in Down's syndrome

M Adorno et al. **SEE N&V P.325**

385 **PROTEIN FOLDING** Structural insight into the biogenesis of β -barrel membrane proteins

N Noinaj et al.

LETTERS

391 **ASTRONOMY** A strong magnetic field around the supermassive black hole at the centre of the Galaxy

R P Eatough et al.

395 **SOLAR CELLS** Efficient planar heterojunction perovskite solar cells by vapour deposition

M Liu, M B Johnston & H J Snaith

SEE N&V P.323

399 **NANOPARTICLES** Ultrastable silver nanoparticles

A Desireddy et al.

403 **CLIMATE CHANGE** Recent global-warming hiatus tied to equatorial Pacific surface cooling

Y Kosaka & S-P Xie **SEE N&V P.318**

408 **CLIMATE SCIENCE** Rapid cross-density ocean mixing at mid-depths in the Drake Passage measured by tracer release

A J Watson et al.

412 **GENETICS** Germline mitochondrial DNA mutations aggravate ageing and can impair brain development

J M Ross et al.

416 **GENETICS** DNA damage in germ cells induces an innate immune response that triggers systemic stress resistance

M A Ermolaeva et al.

421 **CANCER** Synthetic lethal metabolic targeting of cellular senescence in cancer therapy

J R Dörr et al.

426 **MICROBIOME** Bacterial colonization factors control specificity and stability of the gut microbiota

S M Lee et al.

430 **PARASITOLOGY** Mechanism of *Trypanosoma brucei gambiense* resistance to human serum

P Uzureau et al. **SEE N&V P.322**

435 **IMMUNOLOGY** Evolutionary implications of a third lymphocyte lineage in lampreys

M Hirano et al.

439 **IMMUNOLOGY** Cross-neutralization of four paramyxoviruses by a human monoclonal antibody

D Corti et al.

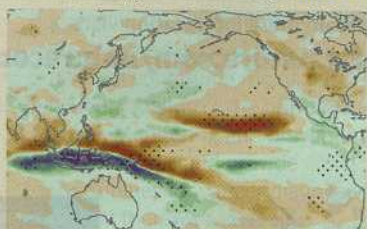
444 **STRUCTURAL BIOLOGY** The structural mechanism of KCNH-channel regulation by the eag domain

Y Haitin, A E Carlson & W N Zagotta

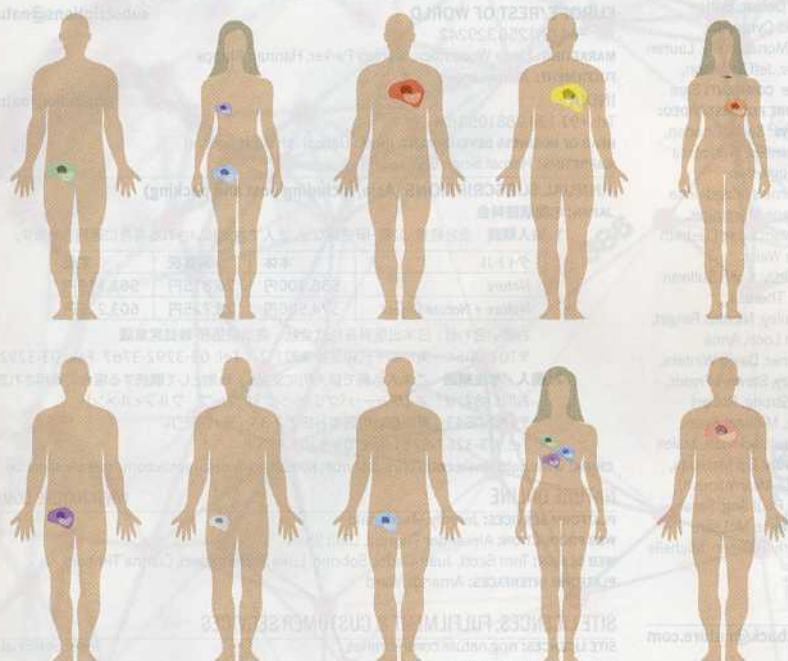
CLIMATE CHANGE

Time out

A bout of Pacific cooling is masking the effects of global warming. **PAGE 403**



TUMOUR HETEROGENEITY



REVIEWS

328 Tumour heterogeneity and cancer cell plasticity

Molecular alterations such as genetic change, as well as differences in the micro-environment, contribute to the functional heterogeneity among cancer cells within a tumour. It has been suggested that the cancer stem-cell model could explain some of this heterogeneity; however, what proportion of tumours follow the model is unclear. Experimental approaches such as cell-fate mapping, transplantation assays and high-coverage sequencing could help to answer this question and uncover the extent to which the model accounts for therapy resistance and disease progression.

Corbin E. Meacham & Sean J. Morrison

338 The causes and consequences of genetic heterogeneity in cancer evolution

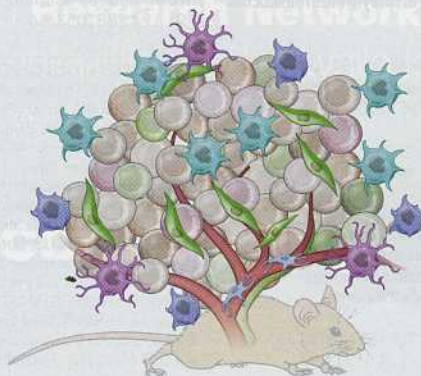
The genetic heterogeneity that exists both between and within tumours affects important cancer pathways and contributes to phenotypic variation. A key cause of genetic

heterogeneity is genomic instability, which leads to increased mutation rates. Understanding the array of mechanisms that result in this instability and their impact on tumour evolution could pave the way to new cancer therapies.

Rebecca A. Burrell, Nicholas McGranahan, Jiri Bartek & Charles Swanton

346 Influence of tumour micro-environment heterogeneity on therapeutic response

A variety of stromal cells, the extracellular matrix, the tumour



vasculature and infiltrating immune cells contribute to tumour heterogeneity. Cancer development and progression are shaped by genetic changes in tumour cells and the fitness advantage these mutations confer in a changing micro-environment. Considering tumours as complete organs rather than a mass of cancer cells is paramount, because the tumour environment can affect response to cancer therapies.

Melissa R. Junttila & Frederic J. de Sauvage

355 Tumour heterogeneity in the clinic

Advances in cancer therapy have been driven by the identification of molecular variations in tumours in different patients. This knowledge can be used to help predict patients' response to targeted therapies. Cancer cells from different geographical locations of the same tumour or its metastases may also vary in their spectrum of molecular and genetic alterations. This interpatient and intratumour heterogeneity make the design of clinical trials that exploit genomic markers challenging. However, taking tumour heterogeneity into account could provide us with a better understanding of therapeutic effectiveness and resistance.

Philippe L. Bedard, Aaron R. Hansen, Mark J. Ratain & Lillian L. Siu

PERSPECTIVE

365 Selection and adaptation during metastatic cancer progression

Disseminated cancer cells that remain after surgery to remove the primary tumour show extensive genetic heterogeneity before metastases eventually appear. This heterogeneity becomes less prominent later, suggesting that disseminated cancer cells become fully malignant as a result of continuing molecular evolution outside of the primary tumour. Monitoring and preventing this evolution could provide opportunities for cancer diagnosis and adjuvant therapies.

Christoph A. Klein