How can journals help to encourage responsible research?

Munich, July 2014

Mark Patterson, Executive Director, eLife

eLIFE

Why did three funders decide to launch a journal?

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Painful peer review

Martin Raff, Alexander Johnson and Peter Walter

Science

"The stress associated with publishing experimental results…can drain much of the joy from practicing science."

End the wasteful tyranny of reviewer experiments

Peer review of scientific papers in top journals is bogged down by unnecessary demands for extra lab work, argues Hidde Ploegh.

nature

Proliferating supplementary files

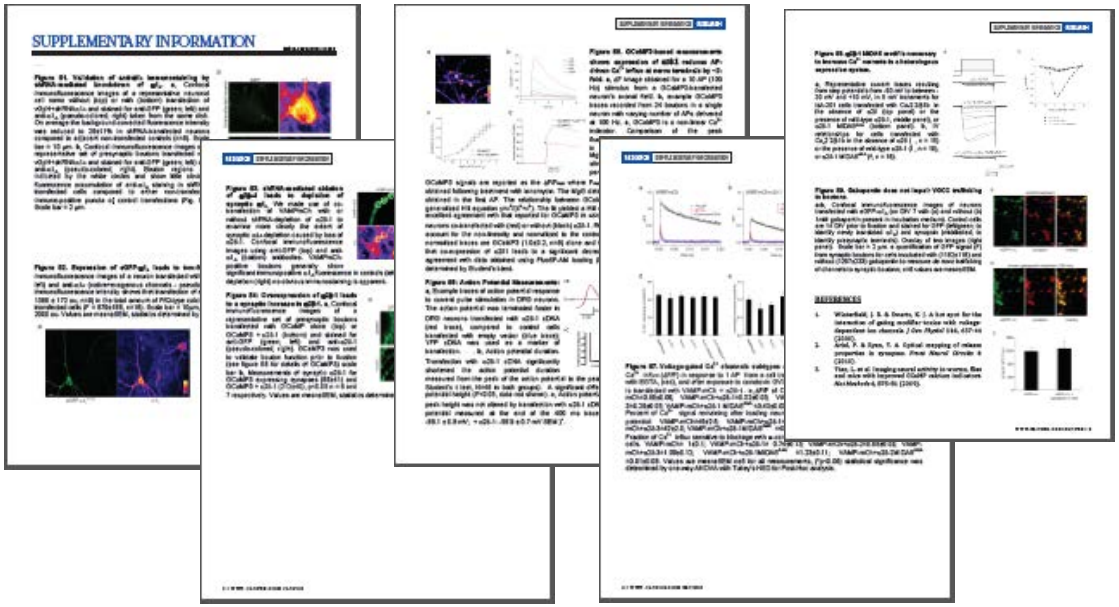
normal sensitivity to EGTA block of exocytosis (Fig. 4d
unable to rescue the decrease in exocytosis resulting fr
data are consistent with the ability of this mutation to bl
heterologous systems[22] (Supplementary Fig. 8), but sh
functioning. Taken together, these results demonstrate
function through at least two separate molecular mecha

Supplementary information

Main • Methods • References • Acknowledgements • Author Information • Supplementary Information

PDF files

1. Supplementary Information (828K)
   This file contains Supplementary Figures 1-9 and Supplementary References.



Unreliable research

Trouble at the lab

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Scientists like to think of science as self-correcting. To an alarming degree, it is not

Oct 19th 2013 | From the print edition

"I SEE a train wreck looming," warned Daniel Kahneman, an eminent psychologist, in an open letter last year. The premonition concerned research on a phenomenon known as "priming". Priming studies suggest that decisions can be influenced by apparently irrelevant actions or events that took place just before the cusp of choice. They have been a boom area in psychology over the past decade, and some of their insights have already made it out of the lab and into the toolkits of policy wonks keen on "nudging" the populace.

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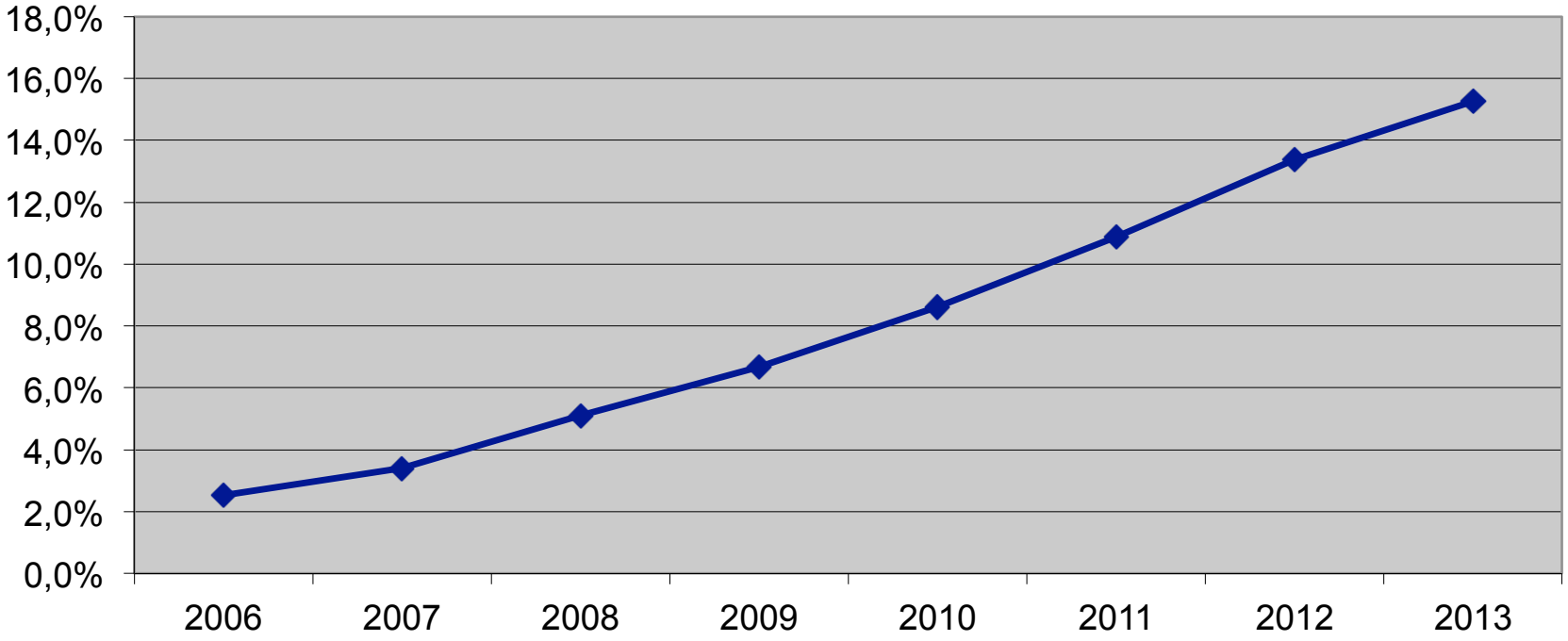

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Plant Growth

CMU 2010 Carnival

Early Universe

Kraus Garden

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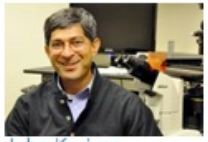
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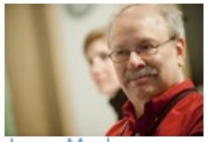
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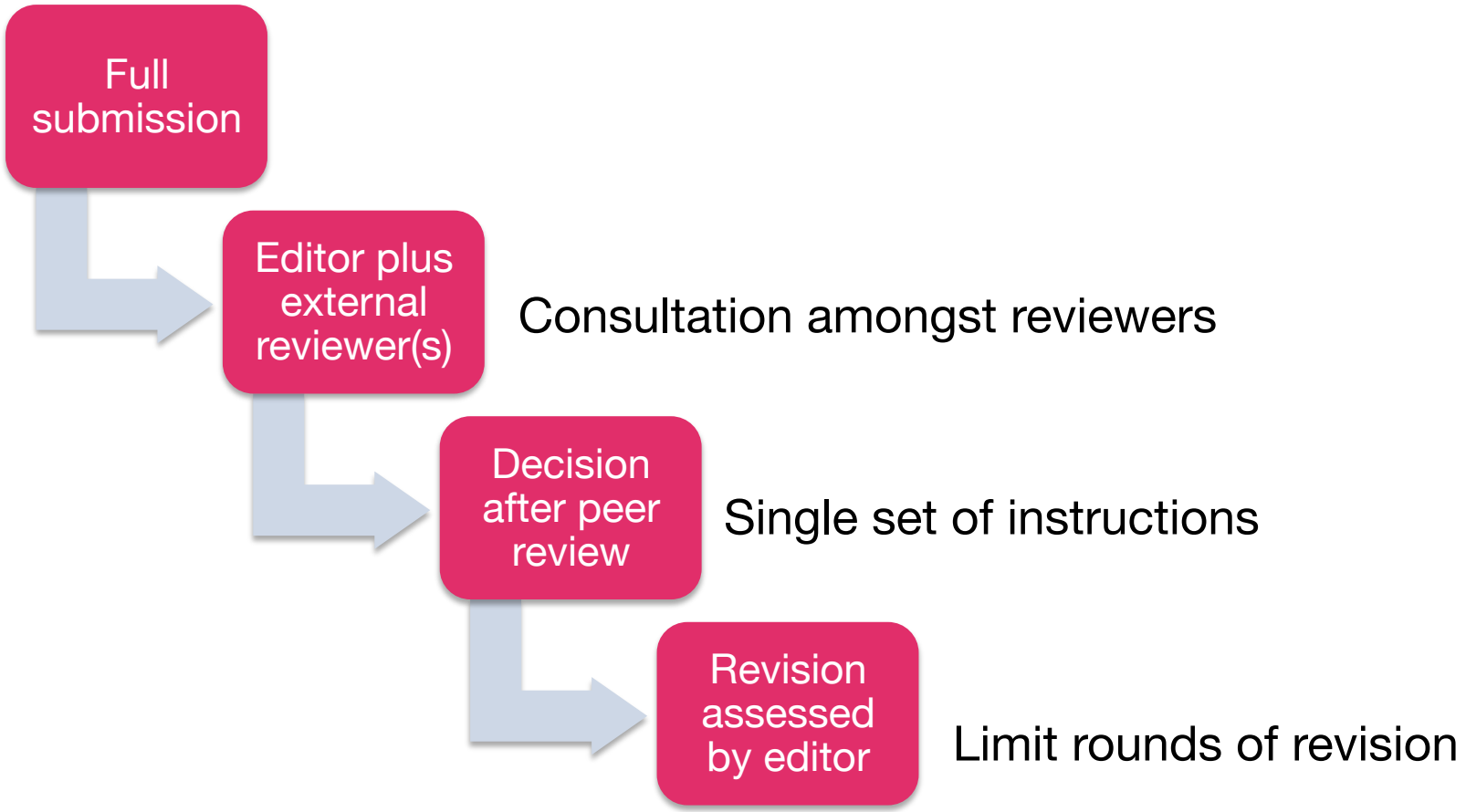
Peer review at eLife



[–] Decision letter

Ivan Dikic, Reviewing editor, Goethe University, Germany

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and a better

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[–] Author response

The main changes from the original submission are as follows:

1. The main criticism of the original submission was that there was not sufficient mechanistic insight into how Cdc48–Ufd1–Npl4 promotes degradation of tUNCs and non-stop decay (NSD) pathway substrates that are translated from messages that lack a stop codon. In particular, we provided no evidence to indicate that the role of Cdc48–Ufd1–Npl4 in this process is direct. In a series of email and telephone discussions with the editors, we were advised that providing evidence to support a direct role for Cdc48–Ufd1–Npl4 in RAD might suffice to address the concern that the reviewers raised about mechanism. We have addressed this criticism by showing in the revised manuscript that Cdc48 and Ufd1 were associated specifically with stringently-washed, affinity-purified ribosomes (Figure 1D). We also show that Cdc48 and Ufd1 bound the NSD substrate GFH^{NS}, but not the control GFH^{Stop} (Figure 3E), despite the latter being present at much higher levels than the NS reporter.

2. In addition to the new figure panels described above (Figures 1D and 3E), we have added the following additional data panels to address the other criticisms made by the reviewers: (i) input controls for Figure 1B, (ii) evidence that accumulation of tUNCs in *cdc48-3* cells is reversed by expression of wild type Cdc48 but not the ATPase-deficient Q2 mutant (Figure 1C), (iii) an expanded Figure 2B to include a control in which RNAse was added to cell lysate prior to isolation of ribosomes, (iv) a new version of Figure 3A showing the effect of *ubr1Δ* and *ltn1Δ* on accumulation of tUNCs in *cdc48-3* mutants, (v) a new version of Figure 3B showing the effect of Cdc48 pathway mutations on accumulation of the NSD substrate GFH^{NS}, including an anti-tubulin loading control, (vi) degradation assays for GFH^{NS} in wild type, *ltn1Δ*, and *ufd1-2* cells and GFH^{Stop} in wild type cells (Figure 3C), (vii) high-resolution sucrose gradient fractionation of lysates of *ltn1Δ* and *cdc48-3* cells expressing PrA^{NS} (Figure 4B; these data replace the sucrose gradient fractionations of GFH^{NS} that were previously shown in Figure 3D), (viii) levels of $Gnd1^{PTC}$ in total cell

RNA-programmed genome editing in human cells

Martin Jinek, Alexandra East, Aaron Cheng, Steven Lin, Enbo Ma, Jennifer Doudna

Howard Hughes Medical Institute, University of California, Berkeley, United States; University of California, Berkeley, United States; Lawrence Berkeley National Laboratory, United States

DOI: http://dx.doi.org/10.7554/eLife.00471
Published January 29, 2013
Cite as eLife 2013;2:e00471

[–] Abstract

Type II CRISPR immune systems in bacteria use a dual RNA-guided DNA endonuclease, Cas9, to cleave foreign DNA at specific sites. We show here that Cas9 assembles with hybrid guide RNAs in human cells and can induce the formation of double-strand DNA breaks (DSBs) at a site complementary to the guide RNA sequence in genomic DNA. This cleavage activity requires both Cas9 and the complementary binding of the guide RNA. Experiments using extracts from transfected cells show that RNA expression and/or assembly into Cas9 is the limiting factor for Cas9-mediated DNA cleavage. In addition, we find that extension of the RNA sequence at the 3′ end enhances DNA targeting activity in vivo. These results show that RNA-programmed genome editing is a facile strategy for introducing site-specific genetic changes in human cells.

DOI: http://dx.doi.org/10.7554/eLife.00471.001

[+] eLife digest

[–] Main text

Introduction

Methods for introducing site-specific double-strand DNA (dsDNA) breaks (DSBs) in genomic DNA have transformed our ability to engineer eukaryotic organisms by initiating DNA repair pathways that lead to targeted genetic re-programming. Zinc-finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs) have proved effective for such genomic manipulation but their use has been limited by the need to engineer a specific protein for each

The rise and fall of the *Phytophthora infestans* lineage that triggered the Irish potato famine

Kentaro Yoshida, Verena J Schuenemann, Liliana M Cano, Marina Pais, Bagdev Rahul Sharma, Chirsta Lanz, Frank N Martin, Sophien Kamoun, Johannes Kraus Thines, Detlef Weigel, Hernán A Burbano

The Sainsbury Laboratory, United Kingdom; University of Tübingen, Germany; Biodiversity and Clim Centre, Germany; Goethe University, Germany; Senckenberg Gesellschaft fü Planck Institute for Developmental Biology, Germany; United States Departm

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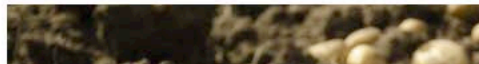

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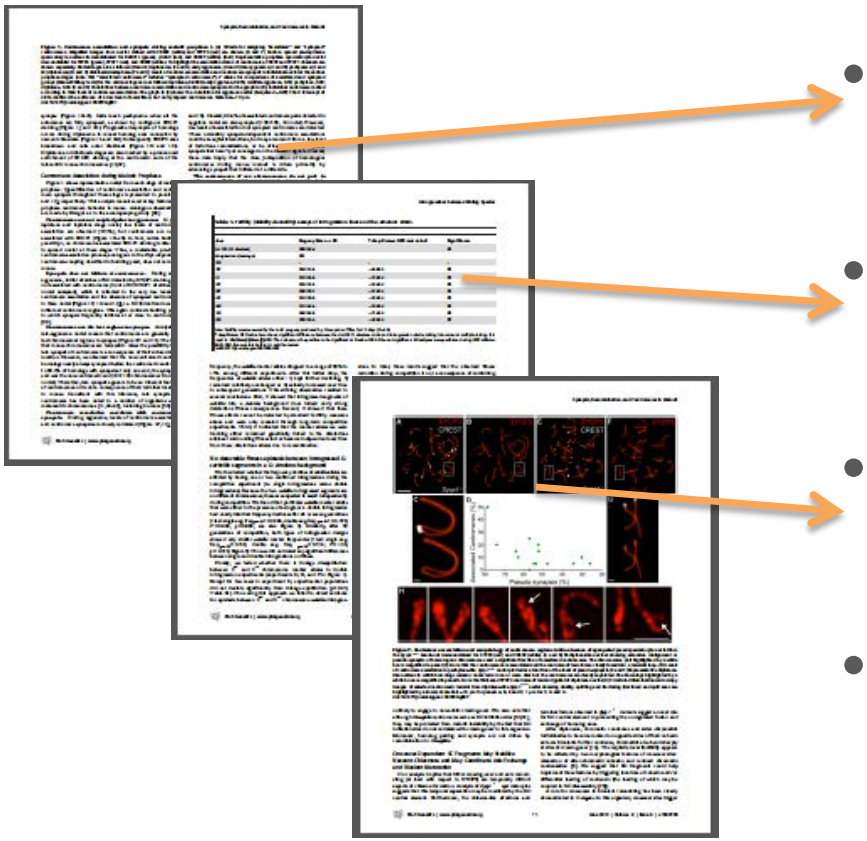

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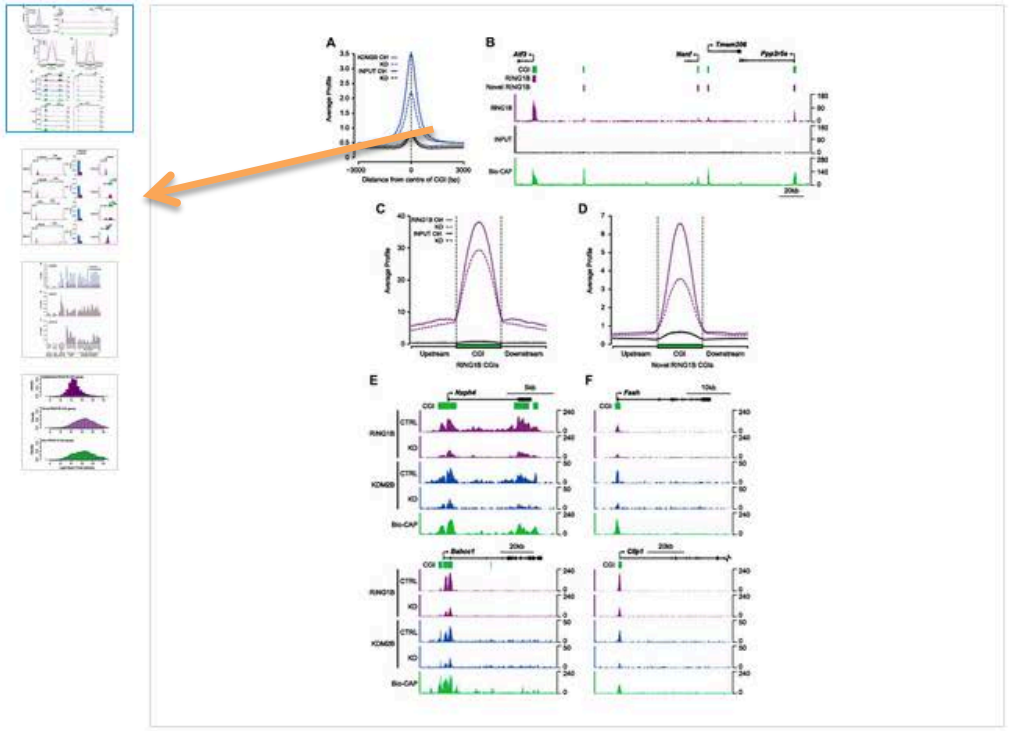
22,849 mouse CGIs genome-wide (Illingworth et al., 2010), and 88% of RING1B occupied CGIs also are bound by detectable levels of KDM2B.



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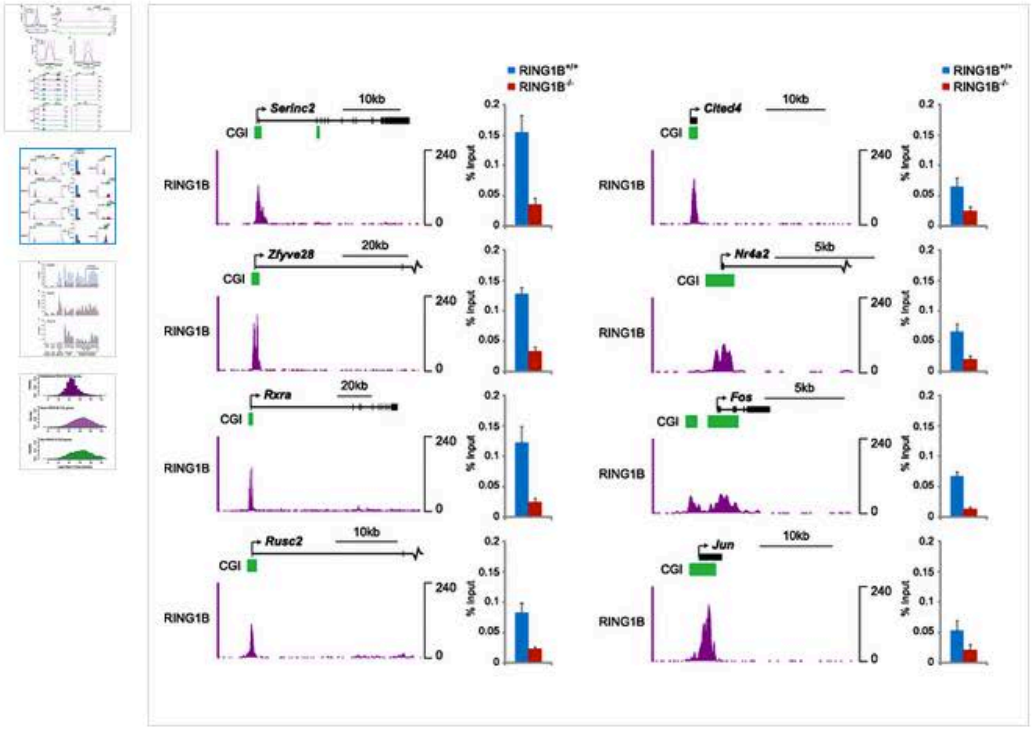
Depletion of KDM2B causes a reduction in RING1B occupancy.

(**A**) KDM2B ChIP-seq signal was plotted at CGIs in the control (solid blue line) and knockdown cell line (dotted blue line). Sequencing signal in the input samples over the same regions are indicated as solid or dotted black lines. KDM2B ChIP-seq signal is specifically lost over CGIs genome-wide in the KDM2B knockdown cell line. (**B**) A snapshot showing RING1B ChIP-seq signal in the control cell line illustrating a previously identified high magnitude RING1B binding sites (i.e. *Atf3*) and novel low magnitude RING1B binding sites. Input sequencing traces over the same region are shown in black. Bio-CAP-seq signal indicates regions containing non-methylated DNA. Above the sequencing traces gene promoters are show by black arrows and exons by vertical black lines. CGIs are shown as

22,849 mouse CGIs genome-wide (Illingworth et al., 2010), and 88% of RING1B occupied CGIs also are bound by detectable levels of KDM2B.



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Conditional removal of RING1B validates the identity of novel peaks identified in the RING1B ChIP-seq.

Eight genes corresponding to novel RING1B peaks identified in ChIP-seq were examined by ChIP quantitative-PCR (bar graphs) in the RING1B conditional ESC cells before (blue bars) and after (red bars) deletion of RING1B by addition of tamoxifen. In all cases deletion of RING1B leads to a loss of RING1B ChIP signal by quantitative-PCR, indicating that these are bona fide RING1B occupied sites. RING1B ChIP-seq traces are shown in each case for comparison. Error bars indicate the SEM for three biological replicates.

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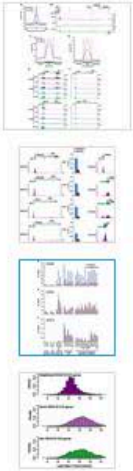
22,849 mouse CGIs genome-wide (Illingworth et al., 2010), and 88% of RING1B occupied CGIs also are bound by detectable levels of KDM2B.



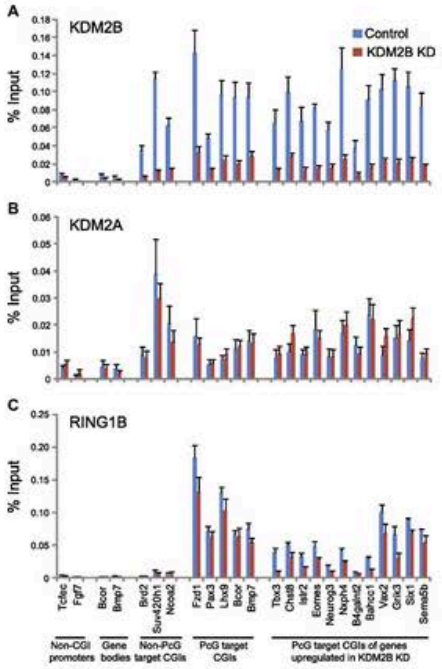


Figure 6—figure supplement 2.

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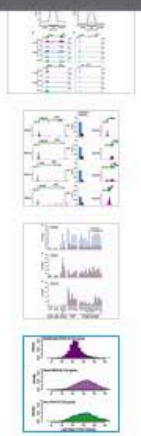
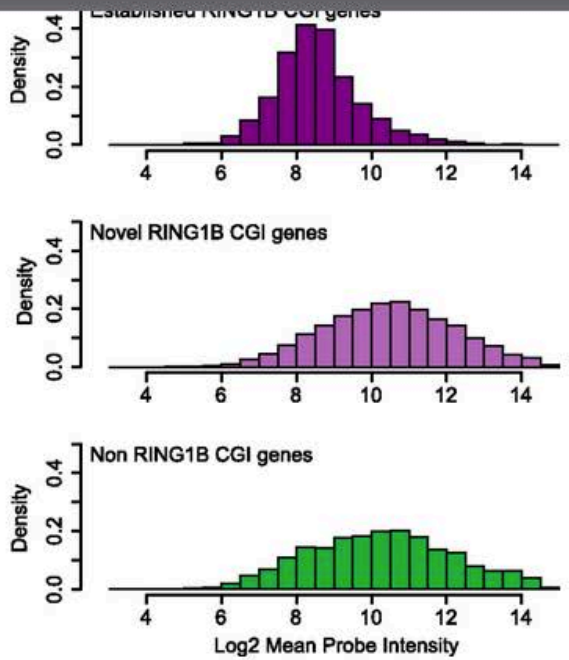
KDM2B depletion results in a loss of RING1B at polycomb associated CGIs.

(**A**) ChIP q-PCR analysis demonstrating that KDM2B depletion results in a clear reduction of KDM2B occupancy at polycomb and non-polycomb CGIs. Error bars represent SEM of three biological replicates (**B**) ChIP analysis demonstrating that KDM2B depletion does not result in major effects on KDM2A occupancy. Error bars represent SEM of three biological replicates. (**C**) ChIP analysis demonstrating that KDM2B depletion causes a reduction in RING1B occupancy at polycomb associated CGIs. Error bars represent SEM of four biological replicates. In all cases ChIP material was analysed by qPCR using primers specific for (i) non-CGI promoters, (ii) gene bodies, (iii) non-PcG target CGIs, (iv) PcG target CGIs, and (v) PcG target CGIs of genes upregulated in KDM2B knockdown cells.





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Genes associated with novel RING1B CGIs are on average expressed at higher levels than genes associated with established RING1B CGIs.

Average microarray signal intensity for genes characterized as associated with established RING1B CGIs (top panel), novel RING1B CGIs (middle panel), and non-RING1B associated CGIs (bottom panel). On average, novel RING1B associated CGI associated genes are expressed at similar levels to non-RING1B associated CGI genes (median signal of 10.47 vs 10.24). In contrast, established RING1B associated CGIs are on average expressed at lower levels (median signal of 8.47).

DOI: http://dx.doi.org/10.7554/eLife.00205.014

To examine whether KDM2B is required for RING1B association with CGIs, RING1B ChIP-seq signal

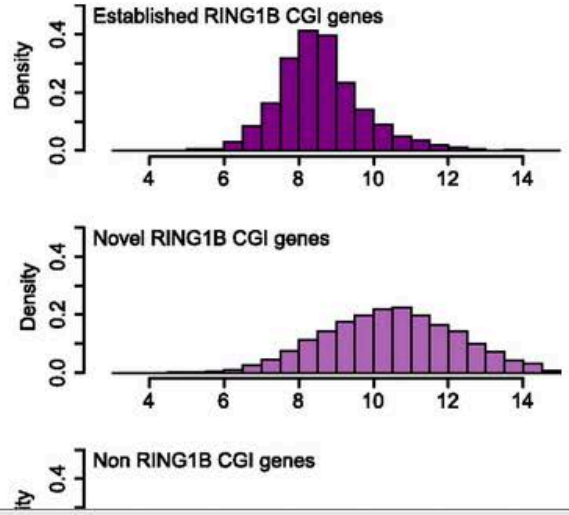
KDM2B links the Polycomb Repressive Complex 1 (PRC1) to recognition of CpG islands

Figure 6—figure supplement 3.

Anca M Farcas, Neil P Blackledge, Ian Sudbery, Hannah K Long, Joanna F McGouran, Nathan R Rose, Sheena Lee, David Sims, Andrea Cerase, Thomas W Sheahan, Haruhiko Koseki, Neil Brockdorff, Chris P Ponting, Benedikt M Kessler, Robert J Klose

University of Oxford, UK; RIKEN Research Center for Allergy and Immunology, Japan

Article DOI: http://dx.doi.org/10.7554/eLife.00205
Figure DOI: http://dx.doi.org/10.7554/eLife.00205.014



Epigenetic conservation at gene regulatory elements revealed by non-methylated DNA profiling in seven vertebrates

Hannah K Long, David Sims, Andreas Heger, Neil P Blackledge, Claudia Kutter, Megan L Wright, Frank Grützner, Duncan T Odom, Roger Patient, Chris P Ponting, Robert J Klose

University of Oxford, United Kingdom; Weatherall Institute of Molecular Medicine, University of Oxford, United Kingdom; Cancer Research UK – Cambridge Institute, University of Cambridge, United Kingdom; The Robinson Institute, University of Adelaide, Australia; Wellcome Trust Sanger Institute, United Kingdom

DOI: http://dx.doi.org/10.7554/eLife.00348
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Abstract

Two-thirds of gene promoters in mammals are associated with regions of non-methylated DNA, called CpG islands (CGIs), which counteract the repressive effects of DNA methylation on chromatin. In cold-blooded vertebrates, computational CGI predictions often reside away from gene promoters, suggesting a major divergence in gene promoter architecture across vertebrates. By experimentally identifying non-methylated DNA in the genomes of seven diverse vertebrates, we instead reveal that non-methylated islands (NMIs) of DNA are a central feature of vertebrate gene promoters. Furthermore, NMIs are present at orthologous genes across vast evolutionary distances, revealing a surprising level of conservation in this epigenetic feature. By profiling NMIs in different tissues and developmental stages we uncover a unifying set of features that are central to the function of NMIs in vertebrates. Together these findings demonstrate an ancient logic for NMI usage at gene promoters and reveal an unprecedented level of epigenetic conservation across vertebrate evolution.

DOI: http://dx.doi.org/10.7554/eLife.00348.001

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Main text

Introduction

Short contiguous regions of non-methylated DNA are found associated with most human and mouse gene promoters, where they create a transcriptionally permissive chromatin environment

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Figures | Major datasets

The following dataset was generated:

Long HK, Sims D, Heger A, Blackledge NP, Kutter C, Wright ML, Grützner F, Odom DT, Patient R, Ponting CP, Klose RJ, 2013.
Epigenetic conservation at gene regulatory elements revealed by non-methylated DNA profiling in seven vertebrates
, GSE43512,
http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE43512
In the public domain at GEO: http://www.ncbi.nlm.nih.gov/geo/.

The following previously published datasets were used:

Mikkelsen TS, Meissner A, Zhang X, Gnirke A, Jaenisch R, Lander ES, 2007.
Genome-wide chromatin state maps of ES cells, ES-derived neural progenitor cells and brain tissue
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In the public domain at GEO: http://www.ncbi.nlm.nih.gov/geo/.

eLife Lens

Quantification of gait parameters in freely walking wild type and sensory deprived Drosophila melanogaster

César S Mendes, Imre Bartos, Turgay Akay, Szabolcs Márka, Richard S Mann

Abstract

Coordinated walking in vertebrates and multi-legged invertebrates such as *Drosophila melanogaster* requires a complex neural network coupled to sensory feedback. An understanding of this network will benefit from systems such as *Drosophila* that have the ability to genetically manipulate neural activities. However, the fly's small size makes it challenging to analyze walking in this system. In order to overcome this limitation, we developed an optical method coupled with high-speed imaging that allows the tracking and quantification of gait parameters in freely walking flies with high temporal and spatial resolution. Using this method, we present a comprehensive description of many locomotion parameters, such as gait, tarsal positioning, and intersegmental and left-right

Contents | Figures | References | Article Info

Figure 1. Image

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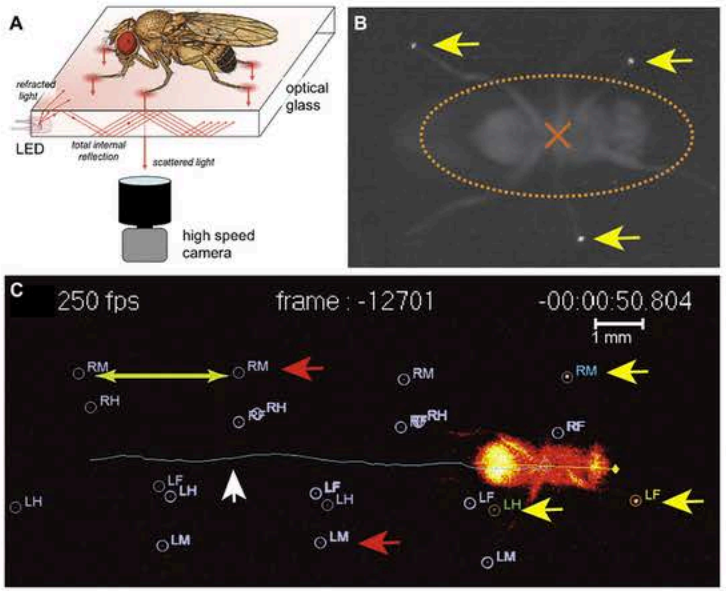

fTIR apparatus and FlyWalker software.

(**A**). Schematic of the fTIR optical effect. LED light sources are located at the edges of an optical glass and light propagates within the glass via internal reflection. Tarsal contacts lead to light scattering detected by a high-speed camera. See Figure 1—figure supplement 1 for more details. (**B**). Single frame of a fTIR video. The fTIR effect can be seen for three legs in stance phase (yellow arrows). Background light partially illuminates the fly's body (orange dashed ellipse; the center of the body is indicated by an orange cross). (**C**). Image generated by the FlyWalker software. The fly's footprints and body center are tracked throughout the video. Present footprints are identified and labeled (yellow arrows). The

High resolution tracking of gait parameters

The analysis of locomotion in large animals, notably mammals, often relies on the placement of visual marks in strategic positions, usually joints that can be readily detected and tracked (Akay et al., 2006). However, in smaller insects such as *Drosophila*, such a strategy becomes not only technically challenging but is also likely to disturb walking behavior and generate artifacts. Such challenges have precluded a more detailed examination of the components that comprise the fly's walking behavior. To overcome these obstacles, and to measure the biomechanical features underlying walking in *Drosophila* we turned to an optical effect known as *frustrated Total Internal Reflection* (fTIR) (Zhu et al., 1986). Total Internal Reflection occurs when light traveling through a medium—in this case optical glass—hits an interface with another medium with a lower refractive index, such as air. If the angle of incidence is above the so-called critical angle (as compared to the normal of the surface), defined by Snell's Law (Katz, 2002), the light is no longer refracted but is internally reflected. For a glass-air interface this corresponds to ~43°. However, if a denser material, such as the tarsus of an insect leg, contacts the surface of the glass, then the locally 'frustrated' total internal reflection will scatter the light, which can be recorded by a high-speed video camera (Figure 1 and Figure 1—figure supplement 1) (Sumriddetchkajorn and Amarit, 2006). A sample video of the unprocessed fTIR effect can be seen in Video 1.

To automate the tracking of the footprints and fly body revealed by the fTIR method, we created a program called FlyWalker that tracks and outputs several user-defined parameters (Figure 1—figure supplement 2). The program, which is freely available for download at http://biooptics.markalab.org/FlyWalker, evaluates the fTIR signals in each

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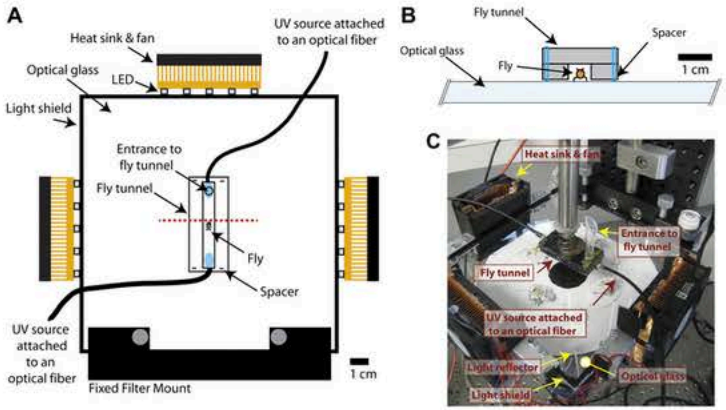
Figure 1–figure supplement 1. Image

mentioned 6 times



Additional information on fTIR apparatus.

(**A**). Detailed schematic of the fTIR apparatus. Red dashed line shows position of the cross-section image in panel (**B**). (**B**) Cross-section of schematic at red dashed line in panel (**A**). (**C**) Photograph of the fTIR apparatus.

DOI: http://dx.doi.org/10.7554/eLife.00231.004

Video 1. Video

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RESEARCH ARTICLE

RNA-programmed genome editing in human cells

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Abstract Type II CRISPR immune systems in bacteria use a dual RNA-guided DNA endonuclease, Cas9, to cleave foreign DNA at specific sites. We show here that Cas9 assembles with hybrid guide RNAs in human cells and can induce the formation of double-strand DNA breaks (DSBs) at a site complementary to the guide RNA sequence in genomic DNA. This cleavage activity requires both Cas9 and the complementary binding of the guide RNA. Experiments using extracts from transfected cells show that RNA expression and/or assembly into Cas9 is the limiting factor for Cas9-mediated DNA cleavage. In addition, we find that extension of the RNA sequence at the 3′ end enhances DNA targeting activity in vivo. These results show that RNA-programmed genome editing is a facile strategy for introducing site-specific genetic changes in human cells.

DOI: 10.7554/eLife.00471

Introduction

Methods for introducing site-specific double-strand DNA (dsDNA) breaks (DSBs) in genomic DNA have transformed our ability to engineer eukaryotic organisms by initiating DNA repair pathways that lead to targeted genetic re-programming. Zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs) have proved effective for such genomic manipulation but their use has been limited by the need to engineer a specific protein for each dsDNA target site and by off-target activity (Urnov et al., 2010; Bogdanove and Voytas, 2011). Thus, alternative strategies for triggering site-specific DNA cleavage in eukaryotic cells are of great interest.

Research into genome defense mechanisms in bacteria showed that CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats/Cas (CRISPR-associated) loci encode RNA-guided adaptive immune systems that can destroy foreign DNA (Marraffini et al., 2010; Terns and Terns, 2011; Wiedenheft et al., 2012). In the Type II CRISPR system from *Streptococcus pyogenes*, the CRISPR RNA (crRNA)-guided DNA cleavage (Sapranauskas et al., 2011), Cas9 generates blunt DSBs at sites defined by a 20-nucleotide guide sequence contained within an associated CRISPR RNA (crRNA) transcript (Gasiunas et al., 2012; Jinek et al., 2012). Cas9 requires both the guide crRNA and a trans-activating crRNA (tracrRNA) that is partially complementary to the crRNA for site-specific DNA recognition and cleavage (Deltcheva et al., 2011; Jinek et al., 2012). Recent experiments showed that the crRNA:tracrRNA complex can be redesigned as a single transcript (single-guide RNA or sgRNA) encompassing the features required for both Cas9 binding and DNA-target cleavage (Jinek et al., 2012). Using sgRNA, Cas9 can be programmed to cleave double-stranded DNA at any site defined by the guide RNA sequence and including a GG protospacer-adjacent (NAG motif (Sapranauskas et al., 2011; Jinek et al., 2012). These findings suggested the exciting possibility that Cas9:sgRNA complexes might constitute a simple and versatile RNA-directed system for generating DSBs that could facilitate site-specific

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Competing interests: See page 8

Funding: See page 8

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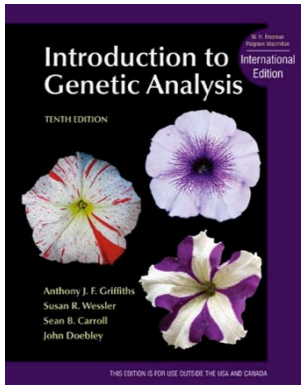

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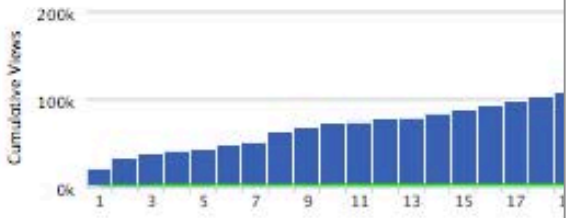

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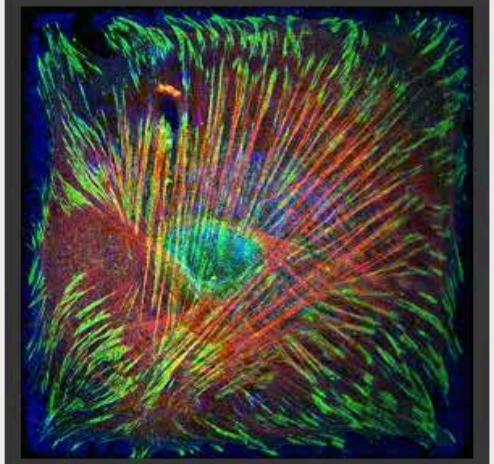

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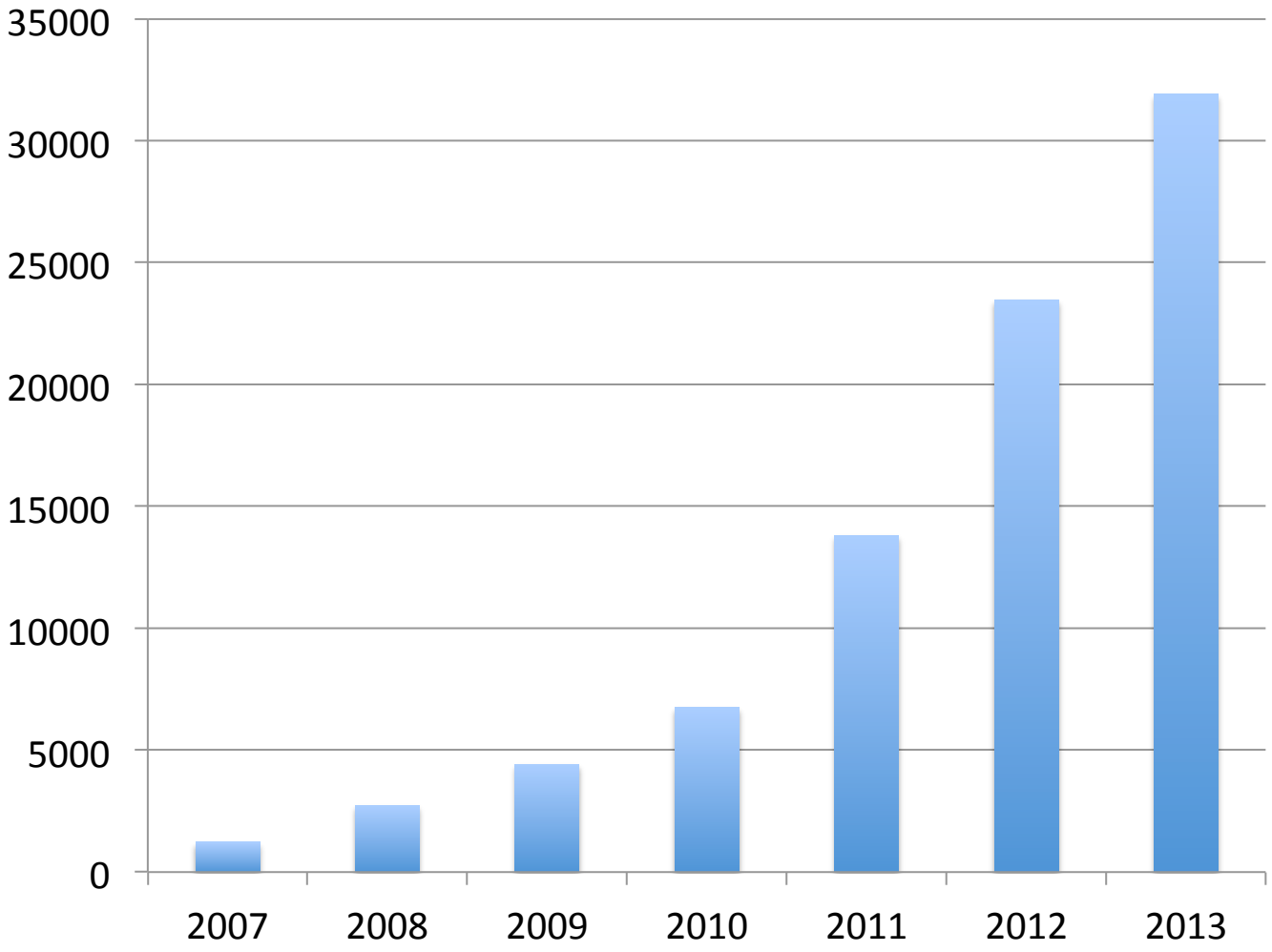

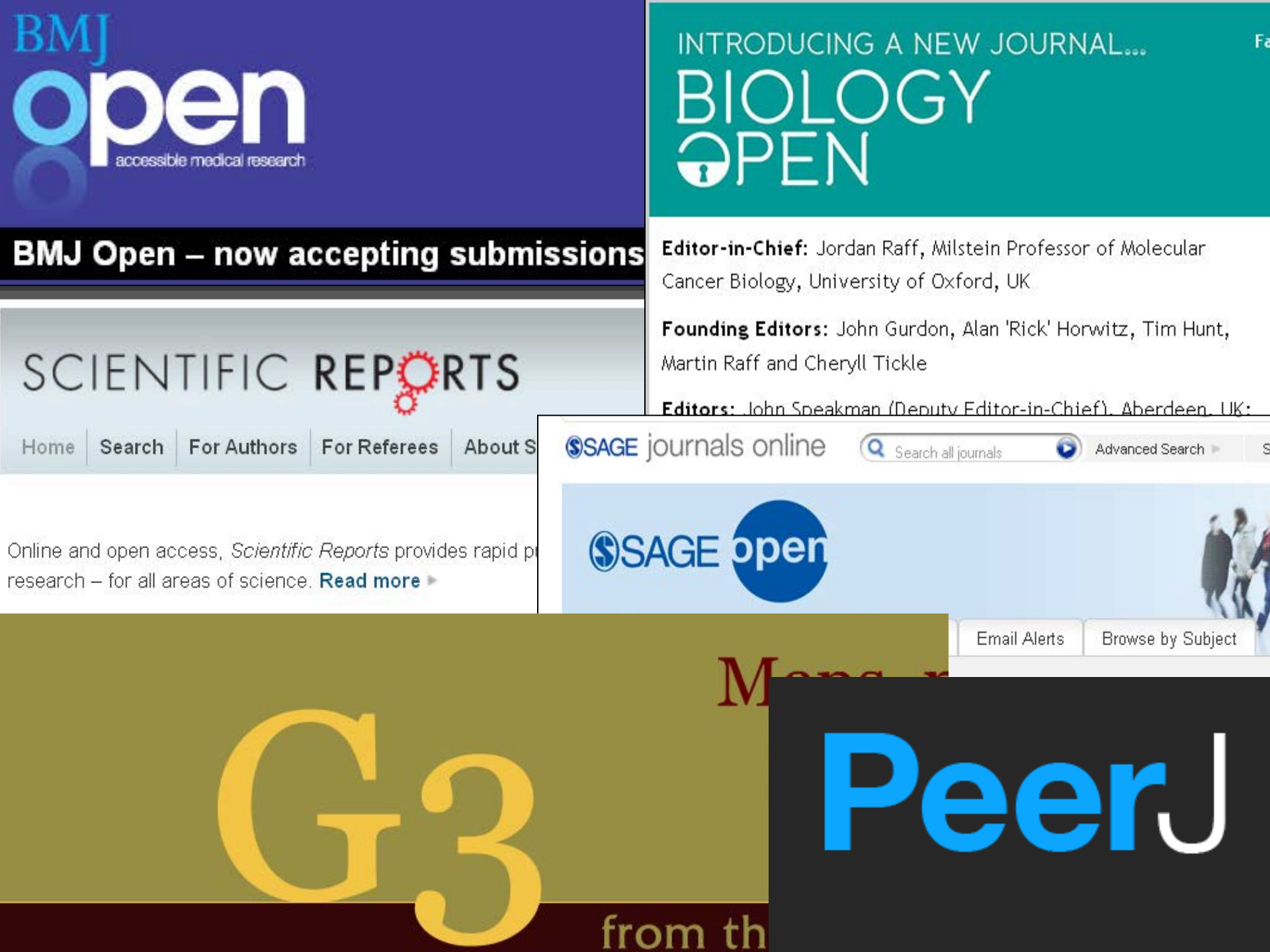
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0 **Unregistered Submission:** (March 24th, 2014 4:12am UTC)

The movies presented in the work look very unnatural. Firstly, nothing is moving at all except for released vesicles. Cell shape, primary cilium, and intracellular vesicles are completely freezing. Second, all vesicles released from primary cilium are flowing away almost in straight lines, and moving in very thin area without getting away from focal plane (4 um in the work). The behavior of vesicles seems extraphysical. Can anybody explain what happens in the movies?

Reply Report

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Unregistered Submission: (March 24th, 2014 2:51pm UTC)

You are right, it is odd looking. During each movie, the signal in the red channel is completely unchanging (for 1 hr); this is especially noticeable in movie S2, where there is substantial signal from surrounding (non-cilia) cell features. One possibility is that the time-lapse actually shows only the time-dependent changes in the green signal, and that this is overlaid upon a red channel image that was captured only at one time (time 0). There is not sufficient methodological explanation in the Figure legends or Experimental Procedures to answer this.

Also strange is the appearance of bands in Figure S3A. All of the bands seem to have an incredibly similar shape to each other (e.g., an upward-facing "hook" at the right edge). This is true for both strong and weak intensity bands. It might be coincidence, but the lack of variation seems a bit unnatural.

Reply Report

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Peer 1: (March 24th, 2014 8:05pm UTC)

Figure 4E might interest you both.

Post-publication comments began March 24, 2014

Article retracted June 2, 2014

New opportunities to encourage responsible research

- Challenge current academic reward system
- Take full advantage of digital technology to present work in full
- Encourage post-publication review and assessment
- Celebrate the positive as well as weeding out the negative

Thank you

Mark Patterson
m.patterson@elifesciences.org

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- What do I do if I see something problematic in a paper – plagiarism, data manipulation, odd methods?
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- Joint authorship?
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- How to make the most of post-publication peer-review?
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