

A PRESENTATION ON INNOVATING WITH eLIFE: JUNE 2017

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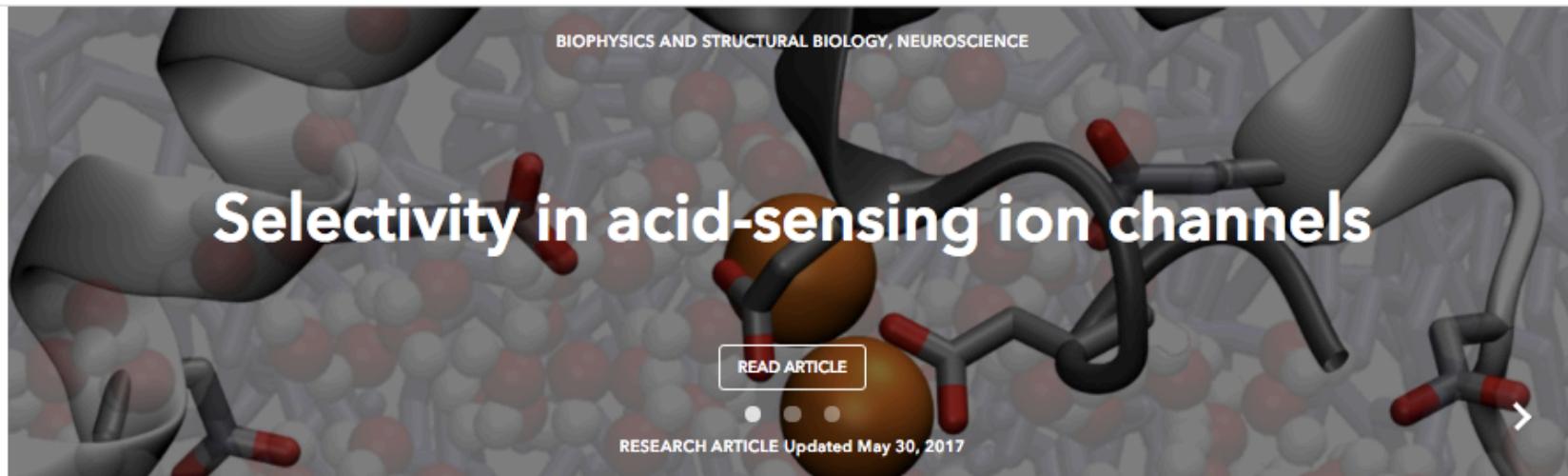
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CELL BIOLOGY, NEUROSCIENCE

A novel ALS-associated variant in *UBQLN4* regulates motor axon morphogenesis

Brittany M Edens et al

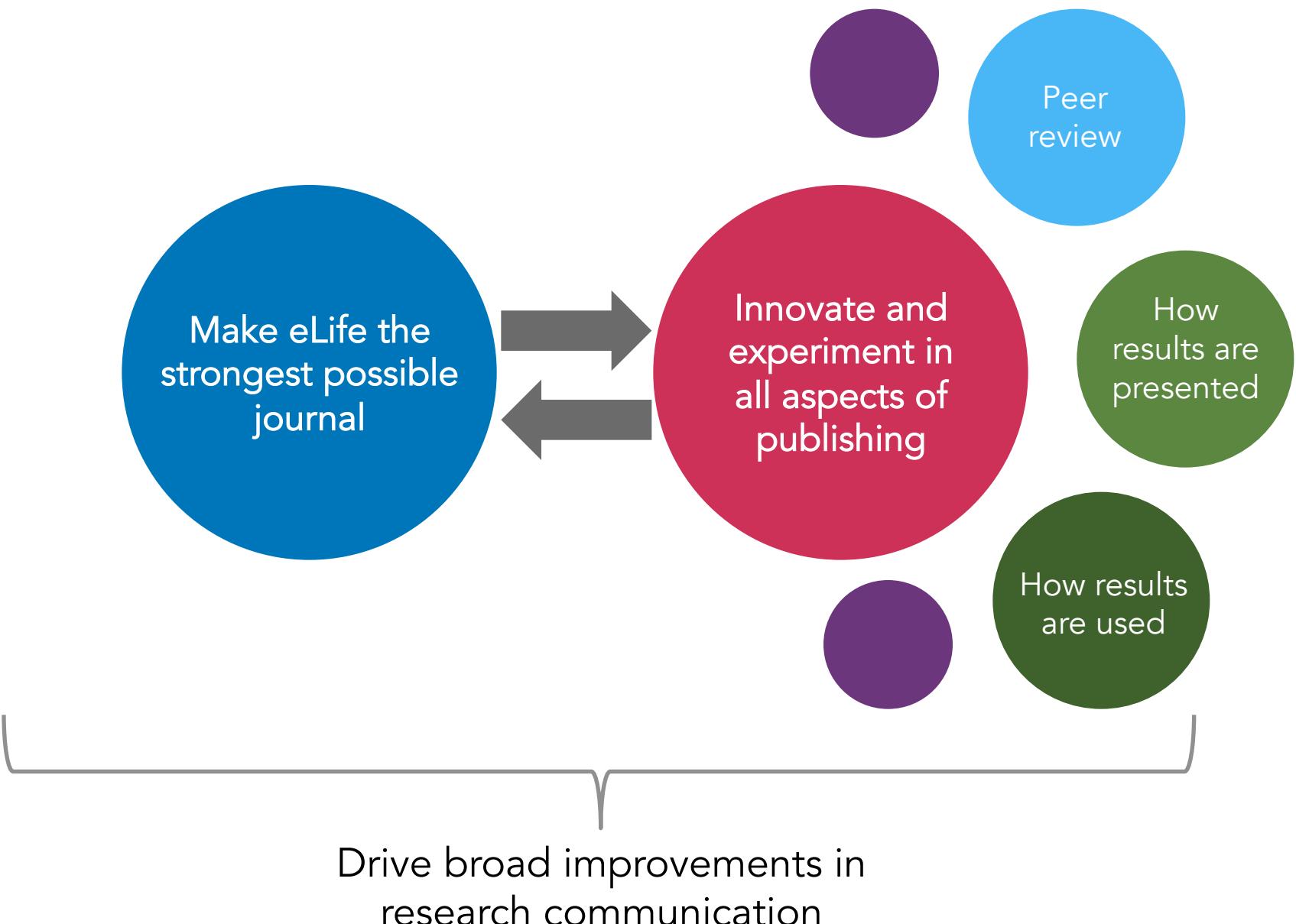
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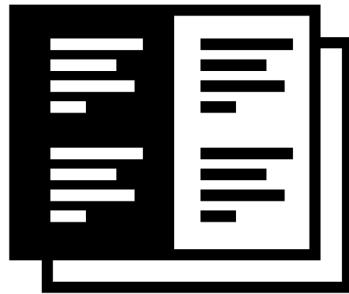
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Dual leucine zipper kinase-dependent PERK activation contributes to neuronal degeneration following insult

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RESEARCH ARTICLE APR 25 2017

DOI: 10.7554/eLife.20725

Abstract

The PKR-like endoplasmic reticulum kinase (PERK) arm of the Integrated Stress Response (ISR) is implicated in neurodegenerative disease, although the regulators and consequences of PERK activation following neuronal injury are poorly understood. Here we show that PERK signaling is a component of the mouse MAP kinase neuronal stress response controlled by the Dual Leucine Zipper Kinase (DLK) and contributes to DLK-mediated neurodegeneration. We find that DLK-activating insults ranging from nerve injury to neurotrophin deprivation result in both c-Jun N-terminal Kinase (JNK) signaling and the PERK- and ISR-dependent upregulation of the Activating Transcription Factor 4 (ATF4). Disruption of PERK signaling delays neurodegeneration without reducing JNK signaling. Furthermore, DLK is both sufficient for PERK activation and necessary for

Abstract

Introduction

Results

- ISR-related expression changes in both PNS and CNS models of axonal damage
- Acute neuronal insults activate PERK
- The ISR influences the mRNA levels of ATF4 target genes after nerve injury
- DLK/JNK signaling is required for PERK activation
- Axonal JNK signaling contributes to PERK activation upon neuronal stress
- Profiling of ISR-dependent gene expression changes following NGF deprivation
- The ISR contributes to neurodegeneration in vitro
- DLK- and PERK-dependent activation of the ISR following optic nerve crush
- PERK signaling contributes to neurodegeneration after axon injury

Discussion

Materials and methods

- Mouse models
- Antibodies and inhibitors
- In vivo nerve injury models
- ISRib dosing in adult mice
- Intravitreal injection of adeno-associated viral (AAV) vectors
- Assessment of RGC survival
- Primary neuron culture and NGF withdrawal
- Microarray analysis
- Quantitative RT-PCR (qPCR) analysis
- High-throughput RNA sequencing
- RNA-Seq alignment
- RNA-seq differential gene expression

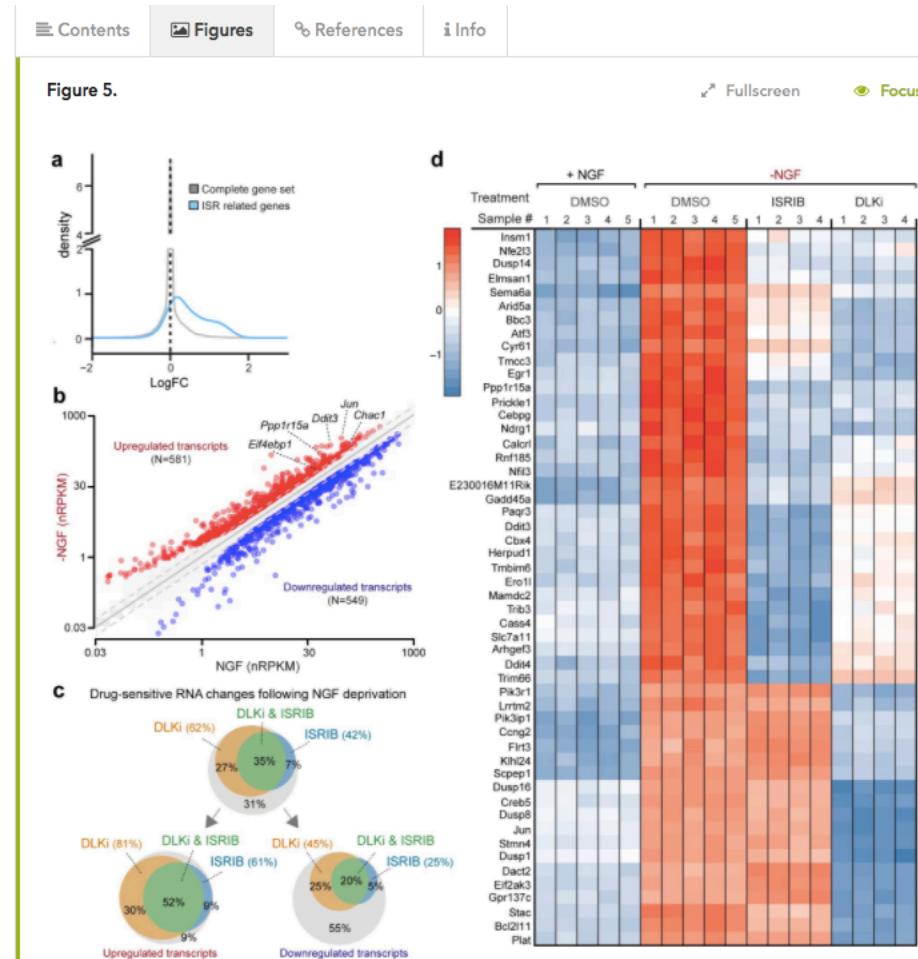
control of ATF4 implied by ISRIB sensitivity and suggest that DLK does not control activation of the ISR primarily through c-Jun-mediated transcriptional changes.

Profiling of ISR-dependent gene expression changes following NGF deprivation

The preceding data argues that ISR activation by PERK represents a previously unappreciated general feature of the DLK-mediated stress response that is more commonly associated with MAP kinase stress signaling. To more broadly examine the relative contribution of DLK/ISR signaling, we performed high-throughput RNA sequencing (RNA-seq) on NGF-deprived cultures of embryonic DRG sensory neurons in the presence of either ISRIB or DLKi (Figure 5).

First, we assessed whether global expression analysis supports the hypothesis that SNC, ONC, and NGF deprivation share the ISR as a common feature. Cross-model analysis showed less broad commonality in expression patterns when comparing SNC to NGF deprivation (Figure 5—figure supplement 1) or when comparing ONC to NGF deprivation (Figure 5—figure supplement 2) than we observed when comparing SNC to ONC (Figure 1b). Nevertheless, we found that, as in the ONC and SNC models, an ISR-related gene set representing putative ATF4-dependent transcripts (Lange et al., 2008) is enriched in this neuronal stress model (Figure 5a). We further examined the ISR genes that we had previously evaluated by qPCR, confirming that *Chac1*, *Eif4ebp1*, *Ppp1r15a*, *Ddit3* were, along with *Jun*, among a group of 1130 mRNAs that reached a strict criterion (>1.5 fold, adjusted $p < 0.001$) for expression change following NGF deprivation (Figure 5b and Figure 5—source data 1).

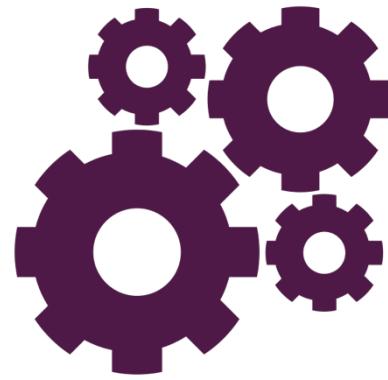
We next examined this group of expression changes for DLK-dependence, finding that about two-thirds were significantly reduced in the presence of DLKi (Figure 5c and Figure 5—source data 1). Further analysis revealed that the DLK-dependence is particularly enriched among upregulated RNAs, with over 80% of the 581 upregulated RNAs exhibiting DLKi sensitivity that reached statistical significance (Figure 5c). Together these findings argue that DLK-mediated stress signaling following NGF deprivation contributes more prominently to induction of stress responsive genes than to downregulation of neuronal gene expression (e.g., the transcription factor *Pou4f2*), distinct from the influential role of DLK in both up- and down-regulated mRNAs previously observed in ONC (Watkins et al., 2013).



RNA-seq reveals ISRIB- and DLK inhibitor-sensitive expression changes following NGF deprivation.

(a–b) Global expression analysis indicates an enrichment in ISR-related genes upregulated 4.5 h after NGF withdrawal from embryonic DRG cultures in the presence of DMSO vehicle ($n = 5/\text{condition}$). (a) Density plot showing 'ISR-related' genes (blue, see Materials and methods) are more frequently upregulated compared to the distribution of all mRNAs expression changes ('complete gene set') ($p < 1 \times 10^{-5}$, one-tailed Student's t-test). (b) Scatterplot of gene expression levels (nRPKM) in NGF-containing and NGF-deprived samples

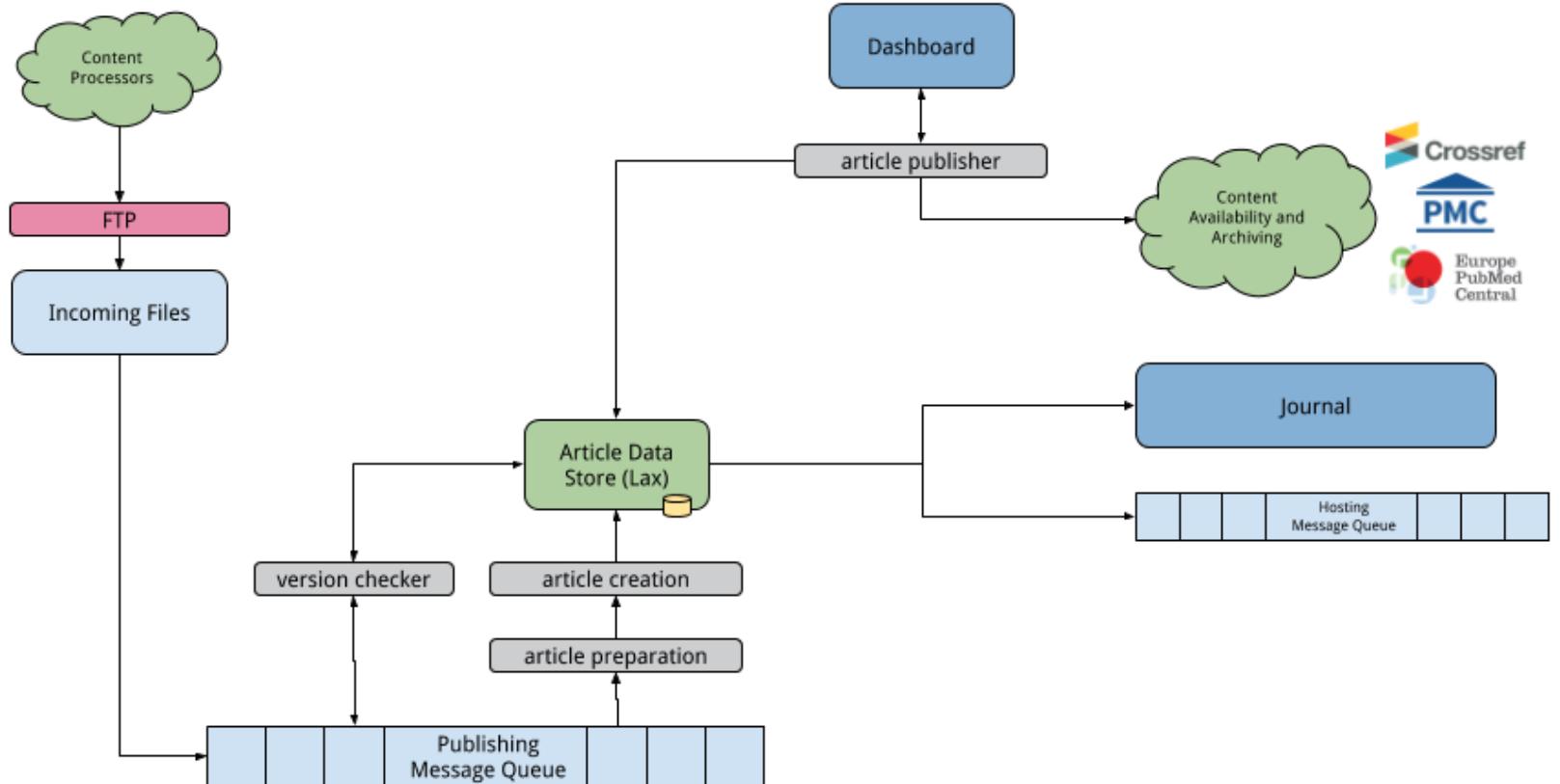
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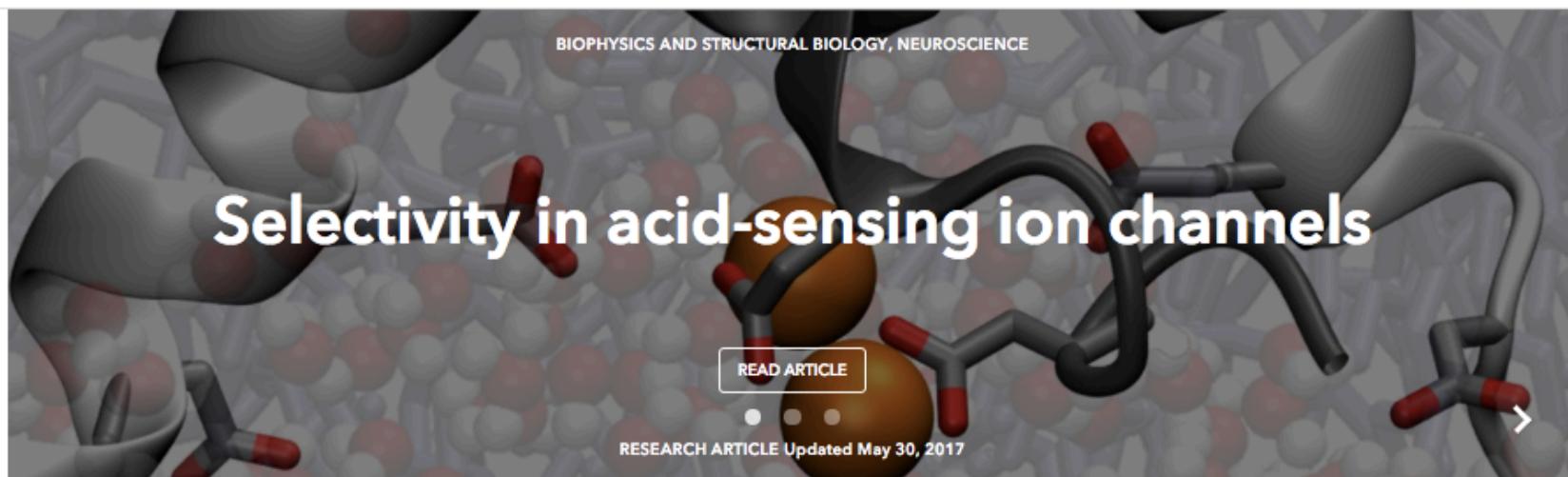


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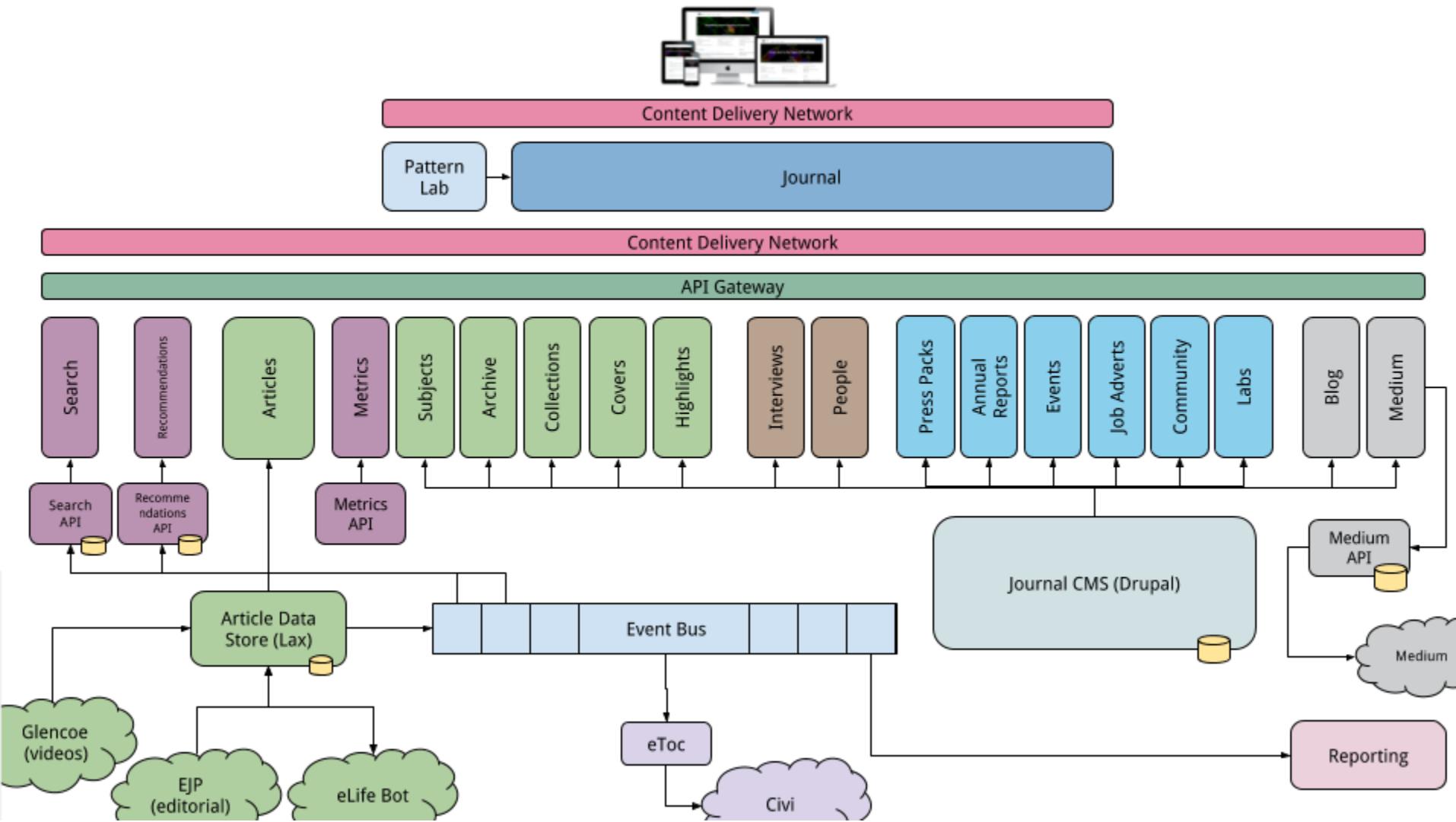
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LABS May 25, 2017



Composing reproducible manuscripts using R Markdown

Chris Hartgerink explains how and why he uses R Markdown to write dynamic research documents.

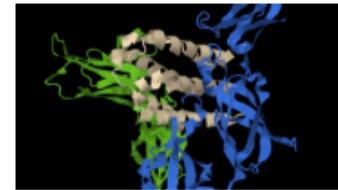
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Hacking new tools for knowledge discovery

At Hack Cambridge Recurse, the eXplore, Knowledge Direct and SciChat projects piqued our interest.

LABS Feb 27, 2017



Sharing macromolecule concepts online with Proteopedia

Scientists from the Weizmann Institute of Science, Israel, showcase the tool they developed to share macromolecules on the web.

LABS Jun 29, 2016



ScienceFair

A screenshot of a mobile application window titled "sciencefair". At the top, there is a search bar with a magnifying glass icon and the placeholder text: "type # to access tagged papers, or *keyword to search local collection". Below the search bar, the main screen displays the text "Search for a paper." in large, dark font. At the bottom of the screen, there is a dark footer bar containing the following information: "offline", "0 results", "18 saved", "1 datasources", and an upward-pointing arrow icon.

Credit: Richard Smith-Unna; Source: <https://github.com/codeforscience/sciencefair>

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 ([Bhaya et al., 2011](#); [Terns and Terns, 2011](#); [Wiedenheft et al., 2012](#)).

The Type II CRISPR/Cas systems require a single protein, Cas9, to catalyze 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 siterecognition ([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 (PAM) 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 genome

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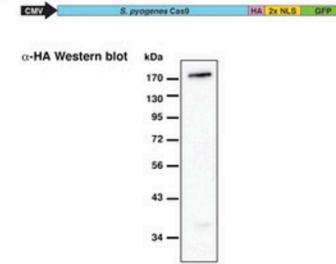


Figure 1.

Fullscreen

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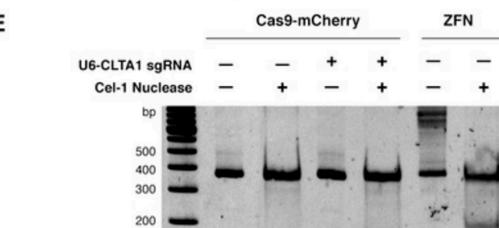
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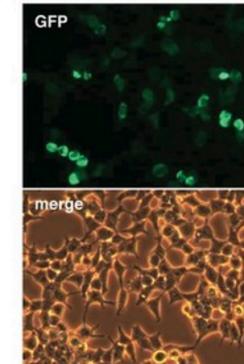
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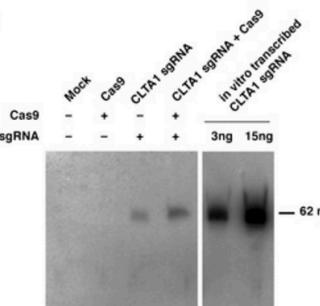
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Longest post onset detection of Zika RNA in semen in multiple case studies

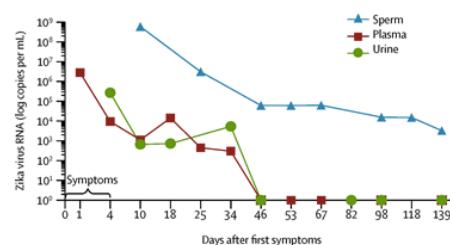
Christa Osuna

Type of test and sample	Results			
	Day 12*	Day 93*	Day 134*	Day 188*
ZIKV real-time RT-PCR serum	Neg	Neg	Neg	NT
ZIKV real-time RT-PCR urine	Neg	Pos (Ct: 36.1)	Neg	NT
ZIKV real-time RT-PCR saliva	Neg (Ct: 36.4)	Pos (Ct: 36.4)	Neg	NT
ZIKV real-time RT-PCR semen	NT	Pos (Ct: 29.6)	Pos (Ct: 32.5)	Pos (Ct: 30.2)
IFA ZIKV IgM titre	1:60	1:40	1:20	1:20
IFA ZIKV IgG titre	1:60	1:20	1:20	1:40
MNT antibody titre	1:60	at 320	at 320	NT

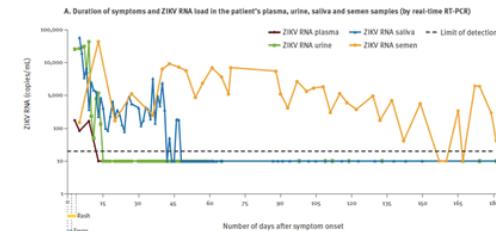
*Number of days after symptom onset.

Laboratory findings related to Zika virus infection in a traveller returning from Haiti to Italy, Feb-July 2016

Nicostri et al
Eurosurveillance



Zika virus in semen and spermatozoa
Mansuy et al
Lancet Infectious Diseases

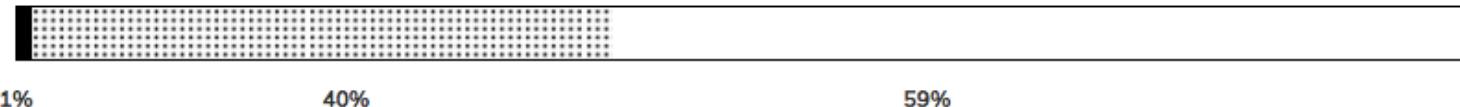


Clinical and laboratory findings in a patient returning from Haiti to Italy, Jan 2016
Barzon et al
Euro Surveillance

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<http://refigure.org/index.html>

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Discussion points

- What frustrates you in your research life?
- How can we best serve you?
- In which new technologies do you see promise?

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discovery in science”**

Randy Schekman, eLife Editor-in-Chief